September 2020
EMA/473607/2020

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

Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

The draft of this module was released for public consultation between 11 December 2019 and 28 February 2020. The module has been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using a specific template.

The comments received are published, 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

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
AESGP

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The EMA's efforts to provide guidance on good pharmacovigilance practices in special patient populations are supported and we welcome the opportunity to participate in the current stakeholder consultation process. Overall, the recommendations appear reasonable (as most clinical development programs exclude pregnant and breastfeeding population). Nevertheless, they could have relevant impact on established PV activities, such as coding, AE reporting/narratives (SCH), signal evaluations, RMP and PSUR and would also require reflecting whether additional PV activities may or may not be needed (e.g. PASS studies, registries) and if the communication (e.g. label) needs to be improved. In evaluating the document, we noted that there is some topics that requires additional information, while other requires clarification regarding their scope and rationale for their inclusion as follows:	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The guidance recommends the consideration of the adverse pregnancy outcomes definitions in section P.III.A.2., while also recommend the use of MedDRA for case coding in accordance with GVP Module VI (MedDRA terms). To avoid confusion, please consider providing clarification of the expected interaction between both terminologies for the involved PV processes. Considering that the RMP Requirements for the applicant/marketing authorisation holder in the EU differ depending on the marketing authorization application and type of product, it would be appreciated if more guidance is provided in terms of the level of information to be included per RMP and per product type (e.g. full MA application, Generic product etc.). This is of high relevance having in mind the maturity of the product and the available data evidence in the areas of pregnancy and breastfeeding. While we recognize the importance of collecting information on long term pregnancy outcomes, the inherent challenges of this activity and the relevant roles and responsibilities of other members of the healthcare chain need to be addressed in the guidance.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Additionally, in comparison with the current adopted GVP modules (including PPSC I, II and IV), the guideline would benefit from further description the roles and responsibilities of other members of the EU network (i.e. Healthcare professionals, Competent authorities in Member States and EMA) under Section P.III.C., but also regarding topics like the proper advice on effective contraception and conduction of pregnancy prevention programs.	

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)*
Line 68-70		There is no evidence presented in the document to support the following sentence: "Whereas historically, obtaining data from pregnant women on medicine use and outcomes during the post-authorisation phase has been challenging, it is becoming increasingly feasible to access data and generate knowledge on safety in this population." Proposed change: Amend sentence to specify which data is more feasible to access, acknowledging that spontaneous data on use in pregnancy is limited.	
Lines 81-85		**Comment:** While defining the terms for pregnancy outcomes, the guideline makes reference to the ones contained in the WHO-ICD 10 (section P.III.A.2). While MEDRA is optimized for safety regulatory needs including indication, labelling, reporting, product safety surveillance and signal detection, the ICD-10 is optimised for Insurance claims, billing and reimbursement. Using the ICD-10 system instead of MedDRA for outcome of pregnancies would make challenging to use SMQ queries, signal detection systems from the shelf, or VigiLyse to compare findings in domestic data pool with global data pool.	

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		Proposed change (if any): As the draft guidance recommends to be in compliance with the latest version of guidance for MedDRA, the expected interrelation between the WCH-ICD 10 and MedDRA terminology needs further clarification. In case it is intended, we don't recommend the use of WHC-ICD guidance for case coding, as this terminology was developed for different purposes and will add unnecessary complexity to established PV process.	
Lines 110-119		**Comment:** While the mechanism of action of a medicine could be an important factor for its potential teratogenicity, other factors like the administration route and pharmaceutical form should be also considered for products of the same class, before a pharmacological-toxicological class effect can be considered. **Proposed change (if any):** "when assessing potential risks for an active substance, known adverse pregnancy outcomes for another substance of the same class of medicinal products should also consider differences that could be related to the medicine administration route or pharmaceutical form."	

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Line 227		**Comment:** Term birth starts with the completion of the 37th week of gestation. Additional wording is proposed to provide clarity on the term definition. **Proposed change (if any):** ***Term birth***: Birth at any time from completed 37 to less than 42 completed weeks (259 to 293 days) of 227 gestation.	
Lines 280-292		**Comment:** GVP Module V states that "if the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information in the RMP". In line 288 it is stated that "relevant knowledge gaps regarding risks associated with the use in pregnancy and/or breastfeeding should be included as missing information". **Proposed change (if any):** We understand that Rev 2 of module 5 allows use of 'missing information' only where the information would be	

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		relevant to the use of the product; it would be helpful to add such clarification here	
Lines 317-319 Lines 340-345 Lines 443-445 Lines 537-538 Lines 609-610		**Comment:** While recognizing the importance of collecting long term appearance information for adverse health outcomes after exposure, the limitations in the process need to be recognized, as this not only includes the participation of MAH´s, but participation from the patients and healthcare professionals. **Proposed change:** For lines 317-319 "…exposure and/or if the suspected medicinal product was taken by the father), should be followed-up to the extent possible in order to collect information on the outcome of the pregnancy and the development of the child after birth." For lines 340-345: "Coding outcomes of exposure during pregnancy is open to ambiguity as a record of 'exposure during pregnancy, resolved' may mean that there is a prospective report of pregnancy exposure and either exposure discontinued, or the pregnancy has ended. Without reporting any further information regarding the pregnancy outcome this is not	

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		helpful. Efforts must be made to report the pregnancy outcome to the extent possible, even if this is not known until long after the exposure occurred and irrespective of whether or not the exposure was discontinued during the pregnancy; For lines 443-445 The child should be followed up to the extent possible to capture the relevant information on health or developmental impact. For lines 537-538 Depending on the outcome of interest, reasonable follow-up efforts may be into preschool or school age, and/or adolescence, as appropriate to reflect the neurodevelopmental outcomes mentioned. For Lines 609-610 In this phase of signal detection and verification, reasonable efforts should be made to confirm detailed information (e.g. timing of gestation, duration, product) regarding exposure during pregnancy	
Line 379		**Comment:**	

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		Header of table for 1st situation is not clear enough. **Proposed change (if any):** Please replace the Header for 1st situation as follows: Adverse Reaction in Mother and	
Lines 390-391		**Comment:** The provision of age specific drug utilisation data represents a challenge, especially for products used during all stages in life. Additionally, women of childbearing age could include paediatric patients that belongs to the "children" or "adolescent" groups as currently adopted in the GVP PSP Paediatrics. **Proposed change (if any):** "Age- and sex-specific drug utilisation data need to be included when possible (in PSUR section 'Estimated exposure and use patterns'), which allows for an understanding of the extent to which the product…"	
Lines 404–405		**Comment:** As the access to information on observational studies sponsored by other MAH´s is limited, we recommend	

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		specifying the scope or the proposed analysis only to the studies under responsibility/sponsorship of the MAH. **Proposed change (if any):** "Data coming from an ongoing or finalised observational study (sponsored by the Marketing Authorisation Holder), e.g. a pregnancy registry, should be analysed a per…"	
Lines 761 - 770		**Comment:** The information to be presented in the table P-III.2 is not clear enough. Also the terms used for the pregnancy outcomes are not consistent with the ones presented in section P.III.A.2. Terminology **Proposed change (if any):** • For "before conception" – guidance of reasonable period of drug intake preceding conception should be provided (e.g. related T1/2 of product), • Does "exposure before conception" includes both father's and mother's exposure? If so, it should be noted in the text. • The terminology (please refer to lines 194-275) provides explanation of multiple terms describing pregnancy outcomes but "foetal defects" are not mentioned at all. We recommend consistency for	

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		terminology used within the proposed GVP guidance. • Its need to be clarified if the information should be presented "cumulative" "for the interval" or both, including clarification in the case more than one table need to be provided.	
Line 824		**Comment:** The date of last menstrual period (LMP) is explained. To determine gestational age, the <u>first</u> day of the LMP needs to be used. **Proposed change:** Replace text in line 824 with the following: First day of last menstrual period (LMP)	
Line 825		**Comment:** The wording for section P.III. Appendix I (Questionnaire), Line 825 "Gestational age at the time of the first contact with MAH") is not consistent with section P.III.B.2. (Reporting of AE), Line 357 "Gestational age at the time of the first contact with reporter should be reported in narrative **Proposed change (if any):**	

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		Please replace wording as follows in the P.III. Appendix I (Questionnaire) as follows: "Gestational age at the time of the reporter first contact with MAH"	
Line 825-827		**Comment:** The wording for section P.III. Appendix I (Questionnaire), Line 825-827:" Gestational age at the time of the first contact with MAH", "Gestational age at the time of drug exposure…" are not consistent with section P.III.B.2. (Reporting of AE), Line 363:" Gestational age when the suspected Adverse Event was observed…" **Proposed change (if any):** To add a new line to the Questionnaire in P.III Appendix 1 as follows: "Gestational age at the time when suspected Adverse Event was observed"	
Line 831-836		**Comment:** In Section P.III. Appendix I (Questionnaire), to namely ask about contraceptive method used will reduce the need for potential follow-up question. **Proposed change (if any):**	

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		To add a new line to the Questionnaire in P.III Appendix 1 as follows: Contraceptive method used	

Please add more rows if needed.

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28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Allergan Limited

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1. General comments

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

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)*
761 – 770		Comment: The CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005) – Annex 3 mentions that "This table must be regarded as the most extended table regarding timing of exposure, data should be provided as available. However, for teratogenic products the table should be filled in completely." Therefore, please clarify the minimum information required to be filled in the table since the information included will be difficult to maintain. Also, please clarify for which products should this table be included in the PSUR. For the teratogenic products, this information would not bring new information due to the already teratogenic profile of the product, and for the non-teratogenic products with pregnancy or breastfeeding related safety concerns in the RMP or the PSUR, please clarify the value this table would bring if the information would not bring new information on the important risks or missing information update during the reporting period. Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment:	

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)*
		Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
APCER Life Sciences 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)*
	PSMF: Considering guidance is related to Population-Specific PV Consideration, there should be specific paragraph dedicated to PSMF/PV System, with following particular: • If Product has pregnancy/lactation specific PV monitoring/aRMM, should be explicitly mentioned in Annex H • In case of pregnancy/lactation specific PV monitoring is additionally performed, a description of the process, data handling and records should be mentioned in PSMF body section of "pharmacovigilance processes".	
	Questionnaire as Routine PV activity: Appendix 1 of this guideline provides questionnaire to collect information on pregnancy exposure. Suggestion to include questionnaire for data collection on drug exposure in nursing mothers and breast-fed infants when considered as missing information in RMP. **Rationale**: Guideline is focussed towards safety in pregnant women. However, safety in breast feeding	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	women and in breast-fed infants is less discussed in the guidance as minimal data availability for this population.	

2. Specific comments on text

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215-216		Comment: Correction suggested below in bold an underlined Proposed change (if any): Termination of pregnancy (induced abortion, elective abortion): Artificial interruption of pregnancy for any reason **prior to independent viability**.	
329		Comment: Correction suggested below in strikethrough and words in bold an underlined Proposed change (if any): Coding of reports of ~~**use a**~~ medicinal product **use** during pregnancy or breastfeeding as follows:	
349		Comment: Correction suggested below in strikethrough Proposed change (if any): As many specific data elements ~~**as**~~ are possible to be obtained should be included in the structured ICH-E2B data elements of the ICSR (see GVP Annex IV) as well as the narrative.	
741		Comment:	

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		Guidance to standard requirements and elements of PPPs can be provided in this document for better clarity as EU Guidelines (GVP Module V and XVI) have has less information.	
754-755		Comment: It should be clarified that both intended and unintended pregnancies should be evaluated for improvement of PPP (suggested text in bold and underlined). Proposed change (if any): In the case of a pregnancy occurring during the use of medicinal product for which a PPP is in place, **pregnancy rates for intended and unintended pregnancies with** the reasons for the occurrence of the pregnancy should be evaluated, where feasible, for the continuous improvement of the PPP.	
761-762		Comment: The sentence refers to table P.III.2 which summarises pregnancy outcome. Therefore, reference to lactation should be removed as proposed below in strikethrough. Proposed change (if any): For all teratogenic products and for those with pregnancy ~~**or breastfeeding**~~ related safety concerns in the RMP or the PSUR, Table P.III.2. should be provided in the PSUR and filled in completely with reporting period interval and cumulative data.	

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796		Comment: In Appendix 1, instruction before questionnaire should also mention the proposed text as below: Proposed change (if any): If aRMMs or PPP is proposed for teratogenic risk, questionnaire should be further elaborated to seek information related to aRMMs or PPP reaching the target population and the collected data should be utilised for effectiveness evaluation of aRMMs in RMP and PSUR.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
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<28 January 2020>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
[redacted], Robert Debré Hospital, Paris, France.

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1. General comments

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

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)*
Line 53		Comment: Consider clarifying that a benefit-risk assessment should be carried out for all medicines/ treatments used in pregnancy, independent of the indication (treatment of unborn child +/- mother) not only when the mother requires treatment.	
Line 59		Comment: Consider adding that the risk of exposure through breast milk should be assessed against the risk of bottle feeding, which may carry different risks depending on the health care setting and social setting (e.g. financial resources for obtaining bottled milk; risk of social exclusion).	
Line 122		Comment: Consider clarifying that the "data about the severity of potential adverse reactions to the medicine in the user population," relates to the breast feeding infant and not the mother	
Line 126		Comment: Consider clarifying that the physiological changes in pregnancy may lead to a change in pharmacokinetics and/or pharmacodynamics, which may lead to either lack of efficacy or dose-related toxicity.	
Line 132		Comment: Consider adding that modelling and simulation and adaptive trials might be considered to determine the appropriate dose in pregnant women. It is also worthwhile noting that PK/PD may change throughout pregnancy and that this should be taken into consideration.	
Line 145		Comment: Consider adding that periconceptional and pre-conceptional drug exposure may also have an adverse effect on the offspring.	
Line 159		Comment: Consider adding that some adverse effects may only become apparent in the next generation (e.g. diethylstilbestrol).	

Line 192		Comment: Consider clarifying that before proceeding to taking a blood sample from a neonate, a neonatal pharmacologist should be consulted and the literature should be searched for evidence. PK analyses need detailed information on the timing of drug administration and relevant covariables such as comedications. If neonatal PK is examined an analysis of maternal serum concentrations and breast milk concentrations need to be included and sampling times need to be recorded. As a first step it might be less invasive to examine whether the drug or its active metabolites are excreted into breast milk. If the drug/ active metabolite is excreted in breast milk neonatal pk sampling may provide information whether the drug/ active metabolite is absorbed by the infant. The benefits of breast-feeding should be weighed against the risk of drug exposure.	
Line 305-306		Specifically the second part of the sentence stating:"*women with heart disease may have an increased risk of giving birth to a child with congenital heart defects due to genetic predisposition*." Comment: Consider clarifying that not all women with heart disease have an increased risk of giving birth to a child with congenital heart defects, because not all heart diseases in adult women are due to a genetic predipostion.	
Line 312		Comment: Consider adding that the RMP should specify whether PK/PD data should be obtained, because as noted above PK/PD may change during pregnancy. In addition, there should be a consideration whether the drug, its metabolites or any of the excipients cross the placenta and how this potentially impacts the offspring. Furthermore, obtaining PK data on excretion into seminal fluid should be considered where appropriate.	
Line 379		Comment: 1st Situation Consider that if there is no adverse event in the child at the time of reporting it would still make sense to have 2 cases (1 mother, 1 baby) as information for the offspring may change with follow up information. For the purpose of summarising cases it would be helpful to have a count of baby cases with no AE reported, but still with a history of in utero exposure (it could be coded as in utero exposure AND no adverse event). These cases are different to a spontaneous abortion or foetal death without information on malformation. Consider clarifying that for multiples (twins, triplets etc.) the same rules apply as for single babies, noting that each offspring should have a separate report and that cross referring all (offspring(s) and mother) is required. It might also be useful to clarify that the same rules apply to ICSRs for breast feeding.	
Line 452		Comment: A number of medical conditions such as for example epilepsy or HIV do require treatment during pregnancy and may harm the offspring. Therefore, the idea of no harm should be clarified. Adaptive and innovative trial design should be considered to answer the question on	

		PK/PD in these women. It is important to consider that not having PK/PD data in these women may also pose a risk of harm to the mother and her unborn child.	
Line 661		Comment: It strikes as unusual to have a RMM recommend how a clinical condition should be managed. How would changing treatment strategies be included in the RMM? Who would develop these recommendations? What would happen it treating neonatologist/ paediatricians do not follow these recommendations?	
Line 687		Comment: Consider repeating/ adding that not all ADRs in the infant might be evident at the time of breast feeding, they may only present much later (e.g. neurodevelopmental delay). As noted above, the benefit-risk of breast vs bottle feeding may need to be considered in the context of the health care setting and social setting.	
Line 697		Comment: Consider adding that in the case of adolescents, age group specific information should be provided (i.e. it is not only that the carers/parents need to be informed, but also and more importantly, the young persons concerned, including their partners)	
Line 728		Comment: In the case of adolescents, age appropriate advice on contraception should be provided and the cultural sensitivities need to be considered.	
Line 886		Comment: Consider adding what kind of data should be collected and reported for clinical trials in pregnant women (for a proposed list see Aurich B, Martin-Montoya T, Zhang D, Jacqz-Aigrain E. Reporting of offspring data in diabetes, HIV infection and hypertension trials during pregnancy: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2019 Oct 9. pii: fetalneonatal-2019-316982. doi: 10.1136/archdischild-2019-316982)	

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February 17,2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Baxter

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	none	

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)*
329-339		Comment: Please clarify if required to code these specific terms as events only when there is an actual AR to the foetus/child during pregnancy/breast-feeding. (GVP VI defines that cases with no harm should not be submitted as ICSRs)	
340-345		Comment: Need clearer guidance on coding of outcome. Outcome for "exposure during pregnancy", should this default to "resolved" since the exposure has occurred?	
760-770		Comment: For all teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the RMP or PSUR, table P.III.2. should be provided in the PSUR and filled in completely with interval and cumulative data. While we understand the request, establishing such table does not seem feasible for cumulative data due to limited information provided in the past and non-searchable data fields in a global database. Proposed change: Limit to interval data	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

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	Outcome *(To be completed by the Agency)*
	The introduction of more guidance on pregnant and breastfeeding women is highly welcomed as these situations always requires specific consideration (and often discussion) as many of the current standards in pharmacovigilance cannot just be applied. However, It seems to be confusing to add another guideline to the already existing CHMP Guideline EMEA/CHMP/313666/2005	
	Alignment in between the GVP modules, in particular with modules V and VII, but also XV and XVI should be established.	
	Comment: Many sections have an informative character but no guidance character. Good and detailed explanations are provided in many sections, but the guidance character is missing – a focus of what is precisely expected by EMA or what has to be done by the MAHs etc. would be desirable. Proposed change (if any): define a goal/aim for each section – is the section only informative or is any action required to be done – define the required action precisely, as there should be no space for different interpretation of the context	

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)*
37		Comment: Too many dots in TOC Proposed change (if any): remove dots	
81-82		Comment: It might be helpful to add why in spontaneous reporting the term AE is used synonymously to (suspected) ADR, i.e. because of the implied causality.	
109		Comment: extrapolation from non-clinical data is also applicable for the mother Proposed change (if any): add maternal ("…knowledge of adverse embryo/foetal and /or maternal reactions of…"	
115-116		Comment: "cannot be extrapolated" appears too strong, as e.g. in pooled plasma products a new product of the same class is not expected to have risks differing from the known class profile Proposed change (if any): "cannot generally be extrapolated"	
117-119		Comment: Exposure through semen is an issue with many uncertainties and is not clear whether there is a general risk at all. Moreover, from practical point of view, data about the father are largely lacking in case reports.	

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)*
		Proposed change (if any): Hence, this issue should be outlined in another separate section, maybe, including some examples under which circumstances this should be considered.	
Insert after line 119 or line 124; Glossary		Comment: The definition of the term "exposure" is as yet missing in the chapter and the modules. While the same standards should be valid for all medicinal products, the methods employed to proof the safety may need to differ. Randomised controlled studies may not be needed in every case. There is a fundamental difference between highly active agents, e.g. known or suspected teratogens, and some niche products such as Art. 14 homeopathic products which "may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy." Considering such basic cornerstones as bioavailability and total dose would be helpful to reduce complexity and ressources. Similar considerations have been employed by e.g. BfArM Graduated Plan on Hypericum (("Abwehr von Gefahren durch Arzneimittel, Stufe II hier: Johanniskraut (Hypericum)-haltige Humanarzneimittel zur innerlichen Anwendung vom 10. Oktober 2005" https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/RisikoBewVerf/q-l/Johanniskraut-Bescheid-051010.pdf?__blob=publicationFile&v=3) and in the Q3D Guideline on Elemental Impurities, EMA/CHMP/QWP/115498/2017.	

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)*
		Taking into account the definition and concept of exposure clarifies that, if clinical trials are not viable, calculations may be an alternative which help both MAHs and assessing authorities. Proposed change (if any): Insert after line 119 or line 124: "Exposure", according to the definition in the WHO IPCS Risk Assessment Terminology . Geneva 2004 (https://apps.who.int/iris/bitstream/handle/10665/42908/9241562676.pdf?sequence=1&isAllowed=y), is the "**concentration or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration.**" In any evaluation, bioavailability issues, including both the route of administration and the total dose administered should expressly be considered. For example, application of the same active substance may result in strikingly different exposure after topical versus oral administration. Likewise, the total doses ingested of homeopathic preparations do usually not result in a measurable plasma level of the original active substance, especially if the criteria for simplified registration are applied (dilution of active substance to 1:10,000 or less). Such basic considerations may be applied even in absence of structured empirical data.	

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)*
168		Comment: Are there any data in terms of how long to follow development of the child to largely exclude embryo/fetotoxic effects Proposed change (if any): If possibly add reference.	
193-275		Proposed change (if any): Add the definition of "Exposure" in section P.III.A.2.Terminology (e.g. after line 193)	
245-263		Comment: add one or two examples to better assign specific medical circumstances to the provided definitions. E.g. under which definition falls a patent ductus arteriosus. Proposed change (if any): Add few examples	
246-252		Comment: Does it make sense to have two definitions that overlapping in many instances? Proposed change (if any): Both, congenital anomaly and congenital abnormality should be merged to have a simpler concept.	
316		Comment: only cases with confirmed exposure should be processed and require follow-up Proposed change (if any): "…embryo or foetus has been exposed…"	

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)*
321		Comment: It is not essential to collect "as many as possible" information but the relevant information. Proposed change (if any): "…and provide any relevant information for all cases…"	
321-322		Comment: There should be discriminate between drugs, which are authorised for pregnancy/breastfeeding and which not. It is hardly expectable that any HCP, who treated pregnant/breastfeeding patient with an authorized drug would report this if no adverse reaction occur in connection with the drug. Proposed change (if any): To reduce effort, spare resource, and assure responsiveness of the reporter, in case of no adverse reaction follow up should focus on unauthorised drugs. For authorised drugs follow up should be performed only in connection with adverse reactions.	
330-335		Comment: P.III.B.2. Management and reporting of adverse reactions states „for the suspected adverse reaction, comply with the latest version of guidance for MedDRA". In case of exposure in pregnancy leading to pregnancy loss or other adverse pregnancy outcomes, the term 'exposure in utero' (LLT Drug exposure in utero, PT Foetal exposure during pregnancy) is recommended for the Reaction/event section. However, the current MedDRA POINTS TO	

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)*
		CONSIDER, section „3.10.2 Events in the child or foetus" states that the LLT to be used in these cases is Maternal exposure during pregnancy. It would be helpful to clarify if this term should be replaced by ‚Drug exposure in utero' or if it should be used in addition to it.	
381-408		Comment: When specific topics should be adressed in e.g. PSURs an update of the respective PSUR GVP should also be considered to avoid scattering of important information over many different documents Proposed change (if any): consider to add a reference/link to this new guideline in other GVP moduls during upcomming updates	
381 ff.		Comment: it is stated that the occurrence of spontaneous reports of adverse pregnancy outcomes should be presented in the PSUR section 'Signal and risk evaluation'. However, unless pregnancy or pregnancy outcomes already constitutes a safety concern/previously recognised risk or a (closed) signal, there is not yet a specific subsection for this topic. Proposed change (if any): It would be helpful if further clarification is provided in which specific section pregnancy outcomes should be presented (or if a new subsection should be inserted).	

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)*
390-392		Comment: Unless, the product is indicated for pregnancy associated indication, such data are only available from the sources mentioned (registries, non-interventional studies). For the vast majority of products and from spontaneous sources such data are largely unavailable. Proposed change (if any): Available information about ICSRs related to pregnancy exposure should be presented in the respective PSUR section.	
396-403		Comment: It is acknowledged that safety during pregnancy or breastfeeding should be described in the PSUR irrespective of whether defined as a safety concern or not. However, where these situations are not defined as a safety concern or missing information the PSUR section "Signal and risk evaluation" does not seem to be the appropriate section as this section should focus on signals and risks only. Proposed change (if any): Since section 9 of the PSUR (Information from other clinical trials and sources) meanwhile contains a subsection on medication errors it seems more reasonable to include an additional subsection on adverse pregnancy outcomes reported spontaneously when this has not been defined as a safety concern in the RMP.	

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)*
		In any way, the proposal to discuss these topics in the PSUR should also be reflected in module VII as well.	
410 ff		Comment: For products indicated for rare diseases and thus with low number of patient's exposure, e.g. orphan drugs, PASS seems not to be an adequate tool for collection the intended data and information. Proposed change (if any): Given that such cases are reported frequently as case reports in medical and scientific literature, a comprehensive review of literature data should be the better tool.	
432-433		Comment: Carrying a PASS in this case would only be ethically justifiable, when the respective medicinal product is indicated for use in pregnancy and/or breastfeeding for the treatment of a disease with unmet medical need.	
635-637; 662-665		Comment: The implementation of RMM in healthcare practice does not only require specific communication skills, we all also need to think about the means to best communicate them in order to achieve the intended goal, and modern ways should at least be considered an option. Unfortunately this is currently not always the case depending on the national authority the topic is discussed with. Proposed change (if any): Add an appropriate statement as regards the means of communication.	

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)*
696		Comment: Materials may also target or an HCP may also involve partners of female patients to communicate risks and RMM. Proposed change (if any): Include "partner" here	
746-748		Comment: Maybe, the clinical circumstances should also be considered. This means, if a drug is only used in only in a specific clearly circumscribed clinical settings and is administered by experienced physicians, a PPP would not be very helpful and would only put burden to patients, authorities, and companies. Proposed change (if any): The special circumstances outlined above should be listed here.	
770 (Table)		Comment: A table is proposed for reporting numbers of pregnancy outcomes for certain medicines. However, it is not specified where this table should be included, e.g. in the PSUR itself or as a separate Appendix. Furthermore it is stated that the table should be filled completely with reporting period interval and cumulative data. Proposed change (if any): It would be helpful if further clarification is provided where the table should be located (e.g. while it might be feasible	

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)*
		to include the table in section 'Signal and risk evaluation' for those substances for which pregnancy/pregnancy outcomes constitute a safety concern this might not be applicable for other substances). Furthermore, clarification would be of interest if the proposed table should be provided twice, once for cumulative and once for reporting interval data, or if both cumulative and interval data should be presented in one table, e.g. similar to the summary table for adverse reactions in the PSUR Appendix.	
902		Comment: This table should be included in module VII as well	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

February 11th 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
CURIUM

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	When the guidelines will come into effect, shall the MAH review all the valid legacy cases included in its global safety database about Pregnant and breastfeeding women, exposure in utero to review and update the coding conventions outlined within this guideline? If yes, in which timeframe this reassessment is expected by the EMA?	
	Is it planned by the EMA to train all the assessors in the Competent authorities to have an harmonise way of assessments about RMPs/PSURs and other PV activities regarding this topic?	
	For products with anticipated use in women of childbearing potential, use in pregnancy and or breastfeeding shall be systematically assigned as missing information in both PSUR and RMP. Could you please confirm this statement?	
	Referring to table P III.1 in the guidelines, when "case" is mentioned, a valid ICSR shall be read instead? Actually, even if the 4 minimum criteria are not met (i.e no adverse event for the mother, 2nd situation last row), a non-valid case is opened (not subject for reporting) and shall be discussed in PSUR and RMP. Is that correct?	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	What is expected by the EMA about long-term pregnancy follow-up on the child? For instance, radiopharmaceuticals products are administered most of the time once in the lifetime of the patient. These patients are administered by nuclear physicians but medically followed by another medical practitioner. In that context, long-term follow-up cannot be performed.	
	Would it be possible to better specify the way to code the outcome (rows 340 to 345) in order to set up harmonised coding conventions?	
	In row 90, it is mentioned that GVP PIII applies in conjunction with GVP module I to XVI. However, is it planned to update according EU GVP module VI because there are currently major discrepancies between these two guidelines? For instance, in module VI the reporting criteria about pregnancy cases are not the same with Table PIII1 of the draft guidelines. Extract from EU GVP Module VI "Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data, or reports which have a normal outcome should not be submitted as ICSRs since there is no suspected adverse reaction"	
	In EU GVP Module VI, the following paragraph outlined: "In certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	to be submitted as ICSRs. This may be a condition of the marketing authorisation or stipulated in the risk management plan; for example, pregnancy exposure to medicinal products contraindicated in pregnancy or medicinal products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin)". Will this section still apply because no mention is made in the draft GVP P III especially in table P.III.1?	
	In GVP P III, the special case of exposure during pregnancy and lactation when contraindicated in the MA is not specified at all, shall this kind of cases be particularly monitored regarding additional risk minimisation measures via the RMP and within the PSUR (new risk in the PSUR if this occured)?	
	Based on the definitions of important identified and potential risks in the EU GVP Module V (RMP) and module VII (PSUR), an exposure of pregnant and breastfeeding women expected within the indications of the product and associated with no undesirable outcome, should not be listed as identified or potential risk but may be listed as missing information. Could you please confirm this assessment?	

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)*
		Comment: Child is missing in first and second situation in Table P III 1. Proposed change (if any): Row 379. In the First row, "child" is missing in the sentence "adverse reactions reported both in mother and …" Same issue for the 2nd situation	
		Comment: There is an error of reference in row 692 Proposed change (if any): PPP (see P.III.B.7.3)	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2020-02-28

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Duchesnay Inc.

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The present comment is related to who we are and not to the draft GVP guideline currently under public consultation: We are a non-EU Pharmaceutical Manufacturer/Market Authorization Holder marketing health products in North America through license-in agreements with EU manufacturers. We also manufacture Health Products for use in the EU through license-out agreements with EU Market Authorization Holders.	
	Availability and analysis of pregnancy outcome and exposure data may vary considerably across the various range of medicinal products. A one-size fits all approach as presented to a certain extent in the proposed guideline (e.g. for pregnancy outcome data collection concepts, completion of Table P.III.2, proposed methods for malformation rate calculations) may not be suitable across all products and greater differentiation vs expectations would be welcome in the final guidance.	
	Medicinal products authorised for pregnancy-related symptoms and disorders, as well as those for which well-conducted epidemiological studies in pregnant women failed to demonstrate a risk to the foetus, were not within scope of the CHMP 2006 guideline	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	which seems to have served as the basis for the creation of the present draft GVP P.III guideline. We are of the opinion that CHMP's example should be followed and such products should equally be exempted in the present proposed guideline. We wish to explicitly outline that exempting those products from the proposed population-specific guideline obviously does not exempt them from the requirements outlined in all other EU GVP Modules in effect, which we believe provide the proper level of safety surveillance mechanisms to ensure continued mother and child's safety with regards to the use of such products. If this proposal is not retained, requirements outlined in the proposed guideline should be adapted to this specific category of products.	

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)*
320-323		Comment: We undeniably acknowledge the importance to collect as many data elements as possible on case safety reports, including cases of exposure during pregnancy and breastfeeding. If our general comment is not retained about exempting from the proposed guideline those medicinal products authorised for pregnancy-related symptoms and disorders, as well as those for which well-conducted epidemiological studies in pregnant women failed to demonstrate a risk to the foetus, we would like for the authorities to acknowledge and include language relative to the limitations encountered in prospective spontaneous post-authorization data collection to the effect that healthcare professionals, due to workload considerations, may not be inclined to invest time in answering phone calls from MAHs or completing lengthy pregnancy outcome forms for such products. In the absence of HCP contribution, MAHs may be required to rely on actual patients (in the situation they are the original reporter) to retrieve pregnancy outcome data to meet the expectations outlined in the proposed GVPs, in which case reliability of the data collected may be limited. In addition, practical experience reveals that inquiring on pregnancy exposure data and authorization to	

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)*
		follow-up to obtain pregnancy outcome data for such products instils undue concerns over the safety of the product in patients' mind, as they tend to become suspicious and worried about taking the product. Proposed change (if any): It is essential that marketing authorisation holders and competent authorities in Member States collect and provide as many elements as possible for all cases~~, irrespective of whether or not a product is authorised for use in pregnancy or breastfeeding,~~ to facilitate the evaluation.	
762 & 770		Comment: We recommend specifying in which section or appendix of the PSUR this information is expected to be included/provided. Would this be the 'Signal and risk evaluation' section? Reference to section P.III.B.3., as relevant, could also be added. Proposed change (if any): For all teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the RMP or the PSUR, Table P.III.2. should be provided in the PSUR section [insert desired PSUR appendix or section name] and filled in completely with reporting period interval and cumulative data.	

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)*
761-764		Comment: Our interpretation of this section as currently written is that Table P.III.2. should be completed and provided in the PSUR irrespective of the product being indicated or not for use during pregnancy, irrespective of it being a teratogen or not, and irrespective of it having pregnancy or breastfeeding safety concerns in the RMP or PSUR. We are hence wondering why make a distinction for teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the RMP or PSUR in lines 761-763 vs all other products under 763-764? Finally, considering this table does not include (rightly so) areas to present information on exposure during breastfeeding, and considering this section focuses on the malformation topic, we propose to remove reference to breastfeeding related safety concerns from line 761. Unless this can be left to the MAHs' discretion, expectations regarding the format to present breastfeeding exposure data could perhaps be covered in a dedicated section. Proposed change (if any): For all teratogenic products and for those with pregnancy ~~or breastfeeding~~ related safety concerns in the RMP or the PSUR, Table P.III.2. should be provided in the PSUR and filled in completely with reporting period interval and cumulative data. ~~For all other~~	

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)*
		~~products, reports on pregnancy outcomes in the list below should be provided as available.~~If no relevant data is available, this should be stated with the rationale provided by the MAH.	
764-766		Comment: We find challenging to decipher expectations regarding calculations of estimated congenital malformation rate. Moreover, we are of the opinion that meaningful malformation rates could hardly be derived from spontaneously (or non-clinical) reported data. If the requirement to provide malformation rate calculations remains in the final guideline, additional language outlining limitations, expectations and rationale to support the decisions behind the proposed calculation method should be detailed. In addition, if our general comment is not retained about exempting from the proposed guideline those medicinal products authorised for pregnancy-related symptoms and disorders, as well as those for which well-conducted epidemiological studies in pregnant women failed to demonstrate a risk to the foetus, it should be mentioned that the overall estimated exposure can serve as the denominator for such products. Proposed change (if any):	

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)*

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
European Association of Hospital Pharmacists (EAHP)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EAHP overall agrees with and welcomes the proposed content of the Guideline on good pharmacovigilance practices for product- or population-specific considerations put forward for pregnant and breastfeeding women.	

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)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
ECHAMP EEIG (European Coalition on Homeopathic & Anthroposophic Medicinal Products)

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement *and* *https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The definition of "exposure" should be explained in the text (see suggestion 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')*	Outcome *(To be completed by the Agency)*
Insert after line 119 or line 124; Glossary		Comment: The definition of the term "exposure" is as yet missing in the chapter and the modules. While the same standards should be valid for all medicinal products, the methods employed to proof the safety may need to differ. Randomised controlled studies may not be needed in every case. There is a fundamental difference between highly active agents, e.g. known or suspected teratogens, and some niche products such as Art. 14 homeopathic products which "may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy." Considering such basic cornerstones as bioavailability and total dose would be helpful to reduce complexity and ressources. Similar considerations have been employed by e.g. BfArM Graduated Plan on Hypericum (("Abwehr von Gefahren durch Arzneimittel, Stufe II hier: Johanniskraut (Hypericum)-haltige Humanarzneimittel zur innerlichen Anwendung vom 10. Oktober 2005" https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/RisikoBewVerf/q-l/Johanniskraut-Bescheid-051010.pdf?__blob=publicationFile&v=3) and in the Q3D Guideline on Elemental Impurities, EMA/CHMP/QWP/115498/2017. Taking into account the definition and concept of exposure clarifies that, if clinical trials are not viable, calculations	

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)*
		may be an alternative which help both MAHs and assessing authorities. Proposed change (if any): Insert after line 119 or line 124: "Exposure", according to the definition in the WHO IPCS Risk Assessment Terminology . Geneva 2004 (https://apps.who.int/iris/bitstream/handle/10665/42908/9241562676.pdf?sequence=1&isAllowed=y), is the "**concentration or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration.**" In any evaluation, bioavailability issues, including both the route of administration and the total dose administered should expressly be considered. For example, application of the same active substance may result in strikingly different exposure after topical versus oral administration. Likewise, the total doses ingested of homeopathic preparations do usually not result in a measurable plasma level of the original active substance, especially if the criteria for simplified registration are applied (dilution of active substance to 1:10,000 or less).	

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)*
		Such basic considerations may be applied even in absence of structured empirical data.	
193-275		Comment: Proposed change (if any): Add the definition of "Exposure" in section P.III.A.2.Terminology (e.g. after line 193)	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28th February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
EFPIA

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement *and* *https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be comple*
	In general, the guidance could be strengthened by more clearly differentiate between drugs with and without a labelling indicated for use in a) pregnant and/or b) during lactation, c) need for male contraception d) indicated for use in children e) indicated for treatment of diseases in women of childbearing potential f) indicated for use in males. In addition, a clear separation between pre- and post-conception would be desired. As stated in the current text, it may seem that the same considerations are needed irrespectively of the label of the specific drug. The Guidance would benefit from a clearer separation between accidental exposure and intended exposure during pregnancy. The Guidance would benefit from acknowledging the challenges of collecting data in pregnant women, particularly when the pregnancy is unexpected. These scenarios can pose difficulties in areas such as inclusion in registries or the collection of follow-up information particularly when the child has not experienced an adverse event.	
	Some topics would require additional information, while other require clarification regarding their scope and rationale for their inclusion as follows: The guidance recommends the consideration of the adverse pregnancy outcomes definitions in section P.III.A.2., while also recommend the use of MedDRA for case coding in accordance with GVP Module VI (MedDRA terms). To avoid confusion, please consider providing clarification of the expected interaction between both terminologies for the involved PV processes. As a general comment, it would be worth adding the terminology for paediatric ages or reference to ICHE11 and using them accordingly and appropriately throughout the document 2 examples of terminologies requiring further clarifications: • Birth defect is used terminology throughout the document, including tables P.III.1 and P.III.2, but it is not defined in section P.III.A.2 Terminology.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be comple*
	• "molar pregnancy" is considered as one of the pregnancy outcomes. However, this is a pregnancy related disease, and the event is linked to neoplasm SOC; and pregnancy related complication SMQ in MedDRA. Please consider correction and ensure alignment throughout the document.	
	Regarding the number of guidance documents to be consulted/comply with regarding pharmacovigilance activities for Pregnant and breastfeeding women, having now information in the following documents: • 2 CHMP guidelines • All GVP Modules (and specifically GVP Module VI), and • this guideline It makes it difficult to capture each and every guidance on these topics and to ensure MAH robustness of related processes. Suggest this future GVP Module supersedes the CHMP guidance and cover for what may be part of these CHMP guidelines and not included yet in this GVP Module. (NB it is acknowledged that some items from CHMP guidance EMEA/CHMP/313666/2005 have already been captured in this draft GVP Module) In order to ensure the clarity of guidance in relation to related GVP modules, the terminology used across GVP modules should be aligned following finalization of this guidance. For example, some modules refer to pregnant women only as a special population (GVP Module VIII and IX), while some modules refer to pregnant and lactating women (GVP Module V and VII), and some modules make no mention of pregnant and breastfeeding women (GVP Module XV). Additionally, in comparison with the current adopted GVP modules (including PPSC I, II and IV), the guideline would benefit from further description the roles and responsibilities of other members of the EU network (i.e. Healthcare professionals, Competent authorities in Member States and EMA) under Section P.III.C., but also regarding topics like the proper advice on effective contraception and conduction of pregnancy prevention programs.	
	Overall, more guidance is provided in this guideline on how to manage information from pregnancy exposure than for exposure through lactation. There is no app 1 bis: questionnaire to collect information during exposure through lactation. Collection of information and quantification of breastfeeding is challenging and variable in individual women and between women (e.g. number of women breastfeeding, variable quantities of breast milk, number of months infant breast fed, exclusively breast fed or supplemented with formula). This information is not captured in the guideline and would be another factor to consider.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be comple*
	It would be helpful to include this challenge in the module as well as what role regulators will play in encouraging HCPs to support and facilitate collection of follow-up data in pregnancy and breastfeeding women. It is important to understand what EMA sees as the accepted study design for breastfeeding outcomes, given lacking both robust data and methodology to study. For example, a pregnancy registry may be able to identify a signal but cannot evaluate the safety concern because all risk factors for the specific outcomes for breastfed children need to be prespecified at the time pregnancy registry is initiated, which is often not feasible.	
	Please clarify in the guideline that biologics may not cross the placenta or enter breast milk the same as small molecules. Immunization clinical studies in pregnant women are conducted with the purpose of immunizing the foetus, other vaccinations are indicated in this population like Flu or tetanus. Vaccines do not cross the placenta, so there is not a true exposure to the medicinal product. It would be useful to add guidance on the specific case of immunization during pregnancy or lactation (e.g. event term coding, route of administration, follow-up requirements).	
	In terms of pregnancy exposure and consequences, there is increasing interest in multigenerational and transgenerational inheritance/transmission of phenotypic features (anomalies of the child that has been exposed *in utero* and that may be transmitted to their descendants). In the below specific comments section, different recommendations have been proposed related to this topic. It would be beneficial to have in this guidance an overview of the risks to the pregnancy of the untreated condition.	
	From the introduction and terminology part is seems that the guideline is applicable from the conception and not before, while we would advise it also addresses the risk of teratogenicity or mutagenicity and impact on gamete. There are already some additional risk minimisation measures in place in the EU (eg. retinoids, mycophenolate) which require additional wash out period, and propose precaution and timelines to be considered before pregnancy or have also warnings for the father. Later parts of this guideline related to epidemiology and risk communication give opportunity to explore or communicate risk during preconception period. To ensure consistency, it is advised that introduction P.III.A would also address further preconception period for both mother and father for the teratogenic risk. It is advised P.III.A would cover also drug exposure through semen, similarly as addressed in P.III.A.1.1.	
	This is basically a comment to E2B R3, to add data elements for structured fields such as 'prospective' or 'retrospective' to allow easier analysis for the regulators and MAHs. The MAH may not always have access to the narrative (e.g. EV cases) while follow	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be comple*
	up may be needed which may end up in follow up of a specific case by a few companies on data that was already initially provided by the reporter which will burden the system.	
	The guidance document is very comprehensive and covers most important aspects in RMP, PASS, PSUR, reporting etc. Different study designs and approaches are mentioned (e.g., drug utilization study, comparative study with existing data, registry studies). However, it is recommended that the application of these studies as a **tiered approach** be not explicitly described. By tiered approach, we mean first using a drug utilization study to first understand whether the medication is used among pregnant women. Then depending on results, applying a comparative safety study.	
	Pregnancy registry has proven to be very challenging to conduct because of the slow enrolment. The guideline does not provide guidance on when and under what circumstance a pregnancy registry should be considered. **Proposed change (if any):** Guidelines or basic principles should be provided on when and under what circumstances a pregnancy registry should be considered. Suggest to also include specific examples for when a registry could be used.	
	Pregnancy registry is not ideal way to collect long-term neurodevelopmental outcomes due to its challenge in retaining patients; if healthy children more likely drop from the registry, the missing data won't occur at random, which will be a problem. It will be clearer if the guidance provides more contexts about how the information collected from less reliable sources will be used. While we recognize the importance of collecting information on long term pregnancy outcomes, the inherent challenges of this activity and the relevant roles and responsibilities of other members of the healthcare chain need to be addressed in the guidance	
	Regarding inclusion of pregnancy and breastfeeding information in PSUR-PBRER, the GVP Module VII states that the main objective of the PSUR-PBRER is to present a "comprehensive, concise and critical analysis of the risk-benefit balance of the medicinal product". The draft guidance to summarise relevant safety information regarding of pregnant and breastfeeding data during each reporting period seems to be inconsistent with the GVP. PSURS are key to summarize information on Benefit Risks ration during the period under review. Both section B3, PSUR, and section C1, operation of the EU network, give instructions on description of risks of medicines during pregnancy and lactation. A consolidation of instructions from these sections would help, especially for requirements in table III.2 for specific presentation and analysis for data collected in pregnant women.	
	In summary, above are the most important and general comments that we would like to be addressed first. Then below are specific comments for your consideration.	

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*
43		**Comment:** Recommendation to highlight in the P.III introduction that spontaneous pregnancy loss or still birth before week 12 is difficult to identify and not recorded in any Electronic Health Record.	
46-47		**Comment:** Requests clarification from EMA regarding the categorization of pregnant and/or breastfeeding women as a "vulnerable population" whereas the FDA clarifies that pregnant and/or breastfeeding women are not "vulnerable" as they are not minors or incarcerated and are capable of making informed decisions. **Proposed change (if any):** Consider describing pregnant and breastfeeding women as an "intricate" rather than "vulnerable" population"	
Lines 53-55		**Comment:** Please consider medicine used to benefit the pregnancy, e.g. medicine for assisted reproduction. **Proposed change (if any):** Except for situations…aims to benefit (unborn) child, or aims to assist conception or embryogenesis, risk-benefit considerations…	
Lines 61		**Comment:** Please considered addition, as proposed below in red. **Proposed change (if any):** …medicine use on breast milk production, composite and excretion also need to be considered.	
62-64		**Comment:** Given FDA's recognition of the limited knowledge of the impact of therapies on pregnant and/or breastfeeding women, clarification is requested from EMA regarding the	

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*
		instances in which safety/efficacy data should be generated for pregnant and/or breastfeeding females in a pre-marketing setting. **Proposed change (if any):** Consider providing an example from HIV or other indications which primarily target women of childbearing potential.	
Line 67		**Comment:** Is use of "safety concerns" throughout the document to always indicate "Important potential and identified risks and Missing information", or it does it refer to "safety issues" to avoid confusion? it should be checked and changed as appropriate **Proposed change (if any):** Define safety concerns or use the appropriate terms throughout the document	
Line 67-70		**Comment:** Not sure in practice that information available on pregnant / lactating women is more available to the MAH, considering that access to these data is limited to spontaneous reports, or to data collection schemes established nationally or by the MAH. It should be acknowledged that this remains a challenging, complex and resource-intensive undertaking and the ability to access good quality data that is clinically meaningful and able to inform the safety profile of a medicinal product remains somewhat limited. This is particularly apparent in the EU where patient registries may be undertaken at a Member State level and the development and implementation of common data models is still evolving. The challenges that remain with collecting post-authorisation data can lead to an increased burden on stakeholders including industry and healthcare professionals, particularly in cases where registries are required to collect data on all pregnant women with the disease as these are not easy to set up, often have numerous operational challenges and result in high cost data collection structures.	

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		Proposed change (if any): Whereas historically, obtaining data from pregnant women on medicine use and outcomes during the post- authorisation phase has been challenging, it is becoming increasingly feasible via national registries or organized data collection schemes established by MAHs to access data and generate knowledge on safety in this population. Spontaneous reporting rates for this information remain low.	
Line 81		**Comment:** The term 'adverse event' cannot be considered synonym to (suspected) adverse reaction since adverse event is an event for which the causal relationship is not yet assessed and even not suspected. Especially in spontaneous reporting where the imply causality is usually considered unless the reporter states the opposite. **Proposed change (if any):** Remove the following: "the term 'adverse event' is synonym to (suspected) adverse reaction and"	
Lines 81-85		**Comment:** While defining the terms for pregnancy outcomes, the guideline makes reference to the ones contained in the WHO-ICD 10 (section P.III.A.2). While MedDRA is optimized for safety regulatory needs including indication, labelling, reporting, product safety surveillance and signal detection, the ICD-10 is optimised for Insurance claims, billing and reimbursement. Using the ICD-10 system instead of MedDRA for outcome of pregnancies would make challenging to use SMQ queries, signal detection systems from the shelf, or VigiLyse to compare findings in domestic data pool with global data pool. **Proposed change (if any):**	

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		As the draft guidance recommends to be in compliance with the latest version of guidance for MedDRA, the expected interrelation between the WCH-ICD 10 and MedDRA terminology needs further clarification. In case it is intended, we don't recommend the use of WHC-ICD guidance for case coding, as this terminology was developed for different purposes and will add unnecessary complexity to established PV process.	
Line 89		**Comment:** Referring to the following statement (Line 89): "GVP P.III applies in conjunction with the GVP Modules I to XVI and does not replace these GVP Modules or introduce regulatory requirements in addition to those already covered in existing Modules", this draft GVP Module introduces some key practical and technical requirements such as table to be included in PSURs, list of key items to be collected for Pregnancy and breast feeding cases, guidance for Pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential in Appendix II: how far are these guidance enforceable	
Lines 117-118, 680-682, and 738-740		**Comment:** It would be helpful to expand and clarify the text related to exposure to the embryo/foetus via semen in several lines of the guideline. Is there any distinction to be made in the following two scenarios: (i) when a man conceives a child while taking the medicine that is teratogenic, where the effect of the drug would be on the genetic material within the sperm that fertilises the egg, which subsequently impacts the development of the embryo/foetus; (ii) when the risk is related to exposure of an existing developing foetus as a result of exposure to the semen from a man taking a teratogenic medicine. Specific guidance in each situation and examples of relevant teratogenic medicines could be helpful. Please provide guidelines for when and how to assess risk of drug exposure through seminal fluid.	

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		Proposed change (if any): Clarify the text and provide examples. It should also be considered that a pregnancy conceived with spermatozoids from a treated male could be at risk if the spermatozoid DNA is likely to be impaired by a drug taken chronically.	
107-110		**Comment**: A key element to differentiate and classify the probability for harm (and category of risks) to the child are still non-clinical studies. We suggest to increase the focus on non-clinical data in this section. **Proposed change (if any):** "Because pregnant women are rarely included in clinical trials at the time of marketing authorisation, assessment of potential risks associated with the use of medicinal products in pregnancy usually relies on the extrapolation from non-clinical data, **which can provide valuable information in order to differentiate and classify the probability for harm and category of risks.** ~~and~~ **Further** ~~on~~, knowledge of adverse embryo/foetal reactions of other products with similar pharmacological properties **can also provide information."**	
Lines 110-119		**Comment:** While the mechanism of action of a medicine could be an important factor for its potential teratogenicity, other factors like the administration route and pharmaceutical form should be also considered for products of the same class, before a pharmacological-toxicological class effect can be considered. **Proposed change (if any):** "Consequently, when assessing potential risks for an active substance, known adverse pregnancy outcomes for another substance of the same class of medicinal products should be carefully	

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		considered, including differences that could be related to the medicine administration route or pharmaceutical form."	
113-115		**Comment**: The notion of class effect should be clarified. One should prefer the notion of mechanism of action as suggested in the same paragraph but not applied here. Indeed, one should not consider the "class" of antidepressant as a single class since some (old) are monoamine oxidase inhibitors (MOA-I), some solely inhibit the recapture of serotonin (SSRIs), some inhibit recapture of norepinephrine and serotonin (SNRIs). Similarly, among anti-epileptic drugs (AEDs), some act via GABA-ergic mechanisms (some being agonist, some inhibiting GABA degradation), some act on the synaptic vesicle protein 2A (SV2A), some are blocking sodium ion channels. If one wants to best characterize the risk of drugs, one should group them by their recognized and well-established mechanism of action. **Proposed change (if any):** Consequently, when assessing potential risks for an active substance, known adverse pregnancy outcomes for another substance **~~of the~~ sharing a** same **~~class of medicinal products~~ mechanism of action (on-target or off-target)** should be carefully considered. However, evidence of absence of harm to the child for one substance cannot be extrapolated to other substances **~~of the same class~~ sharing this same mechanism of action** and be interpreted as indicating the absence of a potential risk for these other substances.	
117-118		**Comment:** The statement says, "It also means 'birth defects' in general should not be studied as one single outcome." Which is very strong. It is understood why birth defect in general is not an idea outcome, which is like studying all-cause mortality or malignancy, but it still provides some useful	

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		information, especially for the following reasons: 1) birth defects including all subtypes are rare events with no sufficient statistical power, 2) the background rate for specific subtype birth defect is largely unknown, and 3) it is difficult to know which organ or multiple ones that the teratogenic agent likely impacts on. With the reasons above, it is still of public health interest, if a composited outcome shows an overall increase in major malformations; in contrast, no increased risk on overall major birth defects does not rule out risks on specific defects because of limitations in the sample size. **Proposed change (if any):** remove this sentence or put into some contexts	
121-122		**Comment**: Preclinical toxicology data are to be taken into account as well. **Proposed change (if any):** estimation of risks for breastfed infants at the time of marketing authorisation may be based on **preclinical toxicology data,** on pharmacokinetic (PK) data, on data about the severity of potential adverse reactions to the medicine in	
Lines 126-128		**Comment**: It is suggested that examples be included of the types of physiological changes that may impact plasma levels of medicines. **Proposed change (if any):** "Physiological changes during pregnancy may result in changes to medicine plasma levels and associated dose-related adverse reactions or under-treatment, either of which could have negative consequences on the pregnancy outcome through their impact on maternal health **e.g. impact on hepatic metabolism, haemodynamic changes.**"	
130-179		**Comment:** Sections P.III.A.1.2. (Adverse events related to physiological changes of pregnancy) and P.III.A.1.3. (Susceptible periods and adverse pregnancy outcomes) contain key information	

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		and figures about physiological changes during pregnancy and in utero child development without references to scientific publications. **Proposed change (if any):** It is suggested that key items are referenced with scientific publications / recognised text books to help support relevance and accuracy of these key information to help MAH review further and have a more accurate and robust approach in the management of pharmacovigilance in these situations	
135		**Comment:** For contraceptive measures, large and small molecules behave differently when given to a pregnant woman (e.g. Bioavailability). **Proposed change (if any):** We recommend delineating important differences between small and large molecules.	
137-139		**Comment:** Requests that EMA also consider that adverse consequences for pregnancy may result from altered maternal homeostasis and/or drug-related effects on the uterus or placenta.	
Line 139		**Comment:** Suggest clarifying language and removing brackets (taking into account a product's PK half-life) **Proposed change (if any):** "The impact of in utero medicine exposure depends on the ability of a medicine to cross the placenta, dose and duration of such exposure as well as the gestational age at which the exposure occurs taking into account a product's PK **elimination** half-life **and pharmacological distribution model.**"	

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*
Lines 141-142		**Comment:** Terminology used should be consistent with that in Section P.III.A.2. Terminology (see line 193 onwards). **Proposed change (if any)**: "Possible negative consequences of exposure include early pregnancy loss **(e.g. due to miscarriage),** ~~births defects~~ (teratogenicity~~)~~, …"	
Lines 141-143 and 155-157		**Comment:** Please add premature birth and abnormal labour progression as a potential consequences of drug use during pregnancy.	
145-154		**Comment:** As the guidance says 'each congenital abnormality has its specific critical period, it is hard to estimate the susceptible periods'. The gestational window as it is written now is very specific. Also, most previous studies have used 12 weeks or first trimester as relevant exposure window for major malformation. Lastly, susceptible exposure window on maternal pregnancy outcomes, e.g. bleeding, preeclampsia etc are not mentioned. **Proposed change (if any):** Gestational week 0-4 → Initial gestational week (e.g. 0-4); Gestational week 4-16 → Early gestational week that is relevant to major malformation, e.g. 4-16 weeks or first trimester; Gestational week 16 to delivery → Later gestational week that is relevant to embryofoetal development (e.g. 16 week to delivery); Late pregnancy or during delivery → Late pregnancy or during delivery (e.g. within 4 weeks prior or during deliverable)	
147		**Comment:** P.III.A.1.3: for the timing of exposure (Gestational week 4-16), there is a reference to organogenesis which should be in line with P.III.A.2. Terminology). Also previous EMA guidance (CHMP The Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data 2005 - ANNEX 4 - DEFINITIONS) stated 12 weeks as the end of the period of organogenesis. Current text states 16 weeks.	

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*
		Proposed change (if any): Gestational week 4-12 (because organogenesis begins at 4 completed weeks and gestational ends at 12 completed weeks of gestation).	
152		**Comment**: Current text states that interference during gestational week 16 to delivery "…mainly causes minor abnormalities…" However, for example ACEi and ARB products causes renal abnormalities that would not generally be considered minor. **Proposed change (if any)**: Gestational week 16 to delivery: during the remainder of the embryofetal period, ~~**although**~~ structural anomalies may ~~**also**~~ **still** occur~~;~~ ~~**interference mostly causes minor abnormalities,**~~ **additionally there may be** impacts on growth or results in transient or permanent functional defects such as neurodevelopmental disorders.	
Line 155		**Comment:** Late pregnancy should be defined in gestational weeks.	
160-161		**Comment:** Suggest to align term birth with live birth as in P.III.A.2. Terminology. **Proposed change (if any):** "…then only evaluating the frequency of **live** birth defects would underestimate…"	
160-168		**Comment:** It is important to highlight that, when available, additional information should be captured from spontaneous pregnancy loss and stillbirth cases, as for the presence of a congenital anomaly or other adverse outcomes that lead to these fatal outcomes. **Proposed change (if any):** It needs to be recognised that if a major teratogen mostly results in spontaneous pregnancy loss or stillbirth, then only evaluating the frequency of birth defects	

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		would underestimate the teratogenic impact. If available, concomitant information on congenital anomalies should be captured from these two fatal outcomes.	
Line 169		**Comment**: Unclear if the 3% birth defect is referencing major or minor congenital defects. **Proposed change (if any)**: Please cite the national/global statistics reference used and clarify if the 3% is for major or minor birth defects.	
Line 169 and Lines 260-261		**Comment**: If overall, birth defects (line 169) are the same as major anomaly (see line 261) that are visible at birth, suggest frequencies should be aligned at either ~3% or 2-4%, respectively, for consistency. **Proposed change (if any):** Provide either the number (~3%) or range (2-4%) for consistency if the two are the same.	
170-171		**Comment**:"… has been reported …" **Proposed change (if any):** Please include reference	
180		**Comment**: Regarding breastfeeding, the potential for a drug excreted in breastmilk to induce adverse effects in the breastfed infant may depend on the nature of the drug. What is presented in this chapter does pertain to small molecules, but may not apply to biologics, especially monoclonal antibodies or other proteins that may undergo "standard protein digestion" in the child's gastrointestinal tract. **Proposed change (if any):**	

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		The risk to the child can be different depending **on nature of the medicines (e.g. small molecule vs biologic) taken by the mother** or whether the mother takes single dose or few doses, or is under chronic treatment with the medicine, and whether she took the medicine already during pregnancy or initiated treatment during breastfeeding.	
Lines 180-181		**Comment**: It would be helpful to provide a reference to the benefit of pre-clinical studies on breastfeeding in this section. **Proposed change (if any):** Provide reference to the benefit of pre-clinical studies on breastfeeding in this section.	
180-192		**Comment**: As there are differences in the potential of newborn children to metabolise medicines compared to older children or adults, this should be taken into consideration when evaluating the potential impact of exposure through breast-feeding. We suggest that text is added to this effect.	
Lines 186-188		**Comment:** During breastfeeding, additional considerations for the infant should be mentioned, including how the medication may be affected (especially for large molecules) when ingested (e.g. Denaturing of proteins in the stomach, etc). **Proposed change (if any):** Suggest adding additional physiologic considerations for the infant, including how the medication may be affected (especially for large molecules) when ingested (e.g. Denaturing of proteins in the stomach, etc).	
188-189, 588-590		**Comment**: The medicinal product itself will not be excreted in breast milk. Substances of interest should be the active pharmaceutical ingredient, and metabolites thereof if applicable. **Proposed change (if any):**	

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		"PK data of ~~a product~~ **the active substance and/or its metabolite(s)** in breast milk can help inform the level of exposure from breastfeeding." Requests guidance related to pK sampling in breastfeeding infants, i.e. schedule of lab collections/feasibility and challenges of obtaining adequate and repeated blood samples from infants, compliance issues, ethics, etc	
189-192		**Comment**: The data that could be made available in a post-marketing setting, may be very difficult to validate and interpret in such settings (e.g. PK data in child depends on quantity ingested which is usually unknown, timing of sampling and drug exposure may have a big impact on the result). **Proposed change (if any)**: "PK data in a child after intake of a medicine with breast milk provides some information about the possible risk to a child, and when an adverse reaction is suspected in a breastfed infant, it may be valuable to obtain a blood sample from the child. **However, it is acknowledged that this is usually not feasible and the data difficult to validate, analyse and interpret in the routine postmarketing environment.**"	
193 PIIIA2 Terminology		**Comment**: There is an executive summary of the "WHO meeting to develop Brighton collaboration definitions of key terms used for monitoring the safety of immunization in pregnancy" (24-25 July 2014) where the list of events is classified according: 1) Foetal and neonatal events 2) Maternal and pregnancy events In this draft guidance, there is not much emphasis on the pregnant/breastfeeding women as such but mostly on the outcome of pregnancy and the foetus. I would suggest adding some definition concerning the "maternal outcome" or "breastfeeding outcome".	

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		Proposed change (if any): Suggest including as well standard terminology to define "maternal outcome" or "breastfeeding outcome" (e.g.: Preterm Labour, Gestational hypertension, Preeclampsia, Postpartum haemorrhage, etc…)	
193 PIIIA2 Terminology		**Comment**: The guidance references the WHO-ICD 10, see https://icd.who.int/en/; national regulations might be different. The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project has standardized definitions for pregnancy outcomes, recommend to ensure the terminology in here is aligned as the GAIA definitions are being used in vaccine studies of maternal immunization.	
193		**Comment:** Suggestion that the terminology list is provided in an alphabetical order to ease retrieval of relevant information.	
194		**Comment:** It would be appreciated to know the scientific reference for the different stages of pregnancy. **Proposed change (if any):** Please consider adding scientific reference for the different stages of pregnancy.	
Lines 199–201 and Lines 147-150		**Comment**: Definition of 'Embryo' This is defined as between 4 and 12 weeks gestation and is stated to include the organogenesis period. However, Lines 147-150 define the organogenesis period as between 4 and 16 weeks gestation.	

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		Proposed change (if any): Please check to ensure consistency of organogenesis period.	
204		**Comment**: The "narrow" definition of foetus used in this guidance is the scientific definition; whereas the broad terminology is addressing a more lay language definition. **Proposed change (if any):** Please consider to only bring the "narrow" definition of foetus in this guidance, since this is the scientific definition.	
207-208		**Comment:** Suggestion to align definition of pregnancy outcomes with lines 142-143 where also births defects (teratogenicity), foetotoxic effects and delayed adverse events on the developing child are included. **Proposed change (if any):** "***Pregnancy outcome:*** End result of pregnancy, which includes ectopic pregnancy, miscarriage, foetal death, termination of pregnancy and live birth**, births defects (teratogenicity), and foetotoxic effects**.	
Lines 210–213		**Comment**: For the definition of 'Foetal Death', miscarriage is defined as foetal death pre 22 weeks and stillbirth post 22 weeks. However, if a foetal death occurs at 22 weeks gestation, it is not clear whether this would be a miscarriage or stillbirth. Additionally, harmonization of definitions of miscarriage/early foetal death/late foetal death is requested. For example, this may be defined at 20 vs 22 weeks. **Proposed change (if any):** "…Early foetal death (before 22 completed weeks of gestation) is known as miscarriage, whereas late foetal death (**from** ~~after~~ 22 completed weeks of gestation) is known as stillbirth."	

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Line 215		**Comment:** No definition of termination of pregnancy for medical reason **Proposed change (if any) :** Add this term in the definition section can support the analysis of induced abortion for medical reason (potential link to the medicinal product)	
Line 227		**Comment:** Term birth starts with the completion of the 37th week of gestation. Additional wording is proposed to provide clarity on the term definition. **Proposed change (if any):** ***Term birth***: Birth at any time from <u>completed</u> 37 to less than 42 completed weeks (259 to 293 days) of 227 gestation.	
Lines 230-231		**Comment:** Definitions of low birth weight and very low birth weight overlap in weights. **Proposed change (if any):** *"**Low birth weight**:* Body weight of the newborn at birth of **<u>more than 1,499 grams and</u>** less than 2,500 grams (**<u>between 1,500 and</u>** ~~up to and including~~ 2,499 g)."	
234-236		**Comment:** Intrauterine growth restriction (IUGR) and small for gestational age (SGA) should not be used as synonymous. IUGR is used to designate a foetus that has not met its growth potential and is defined as estimated foetal weight (EFW) below the 10th percentile for gestational age. Small for gestational age (SGA) is a term that applies to the infant that is less than the 10th percentile at birth.	

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		Proposed change (if any): Suggest having two distinct definitions.	
Line 239		**Comment:** 'Withdrawal syndrome' is commonly known as Neonatal Abstinence Syndrome. **Proposed change (if any):** Please add '**Neonatal Abstinence Syndrome**' in parenthesis.	
245-263		**Comment:** Definitions could be completed with examples in order to facilitate the understanding of differences between congenital anomalies, abnormalities and malformations. An example could be cited, e.g. it could be based on the Centres for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines (CDC, 2018). The sentence "Terms for defining congenital anomalies (birth defects) are:" is confusing **Proposed Change: Birth defects are defined and include all the terms below:** ~~Terms for defining congenital anomalies (Birth defects) are:~~ • ***Congenital anomaly***: • ***Congenital abnormality:*** • ***Congenital malformation***: • ***Isolated congenital abnormality***: • ***Multiple congenital abnormalities***: • ***Teratogen***: • ***Major***: • ***Minor***:	
Line 249		**Comment:** While the diagnosis of a congenital anomaly can be delayed, it is unclear how the "onset of congenital anomalies can be delayed" (i.e. delayed with respect to?) Given they are congenital, the onset can be either in the embryo or foetus.	

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255-256		**Comment**: Recommendations to add definitions for "multigenerational inheritance" or "multigenerational transmission". The proposed definitions are based on different publications such as Eric E. Nilsson, Ingrid Sadler-Riggleman and Michael K. Skinner - Environmentally induced epigenetic transgenerational inheritance of disease - Environmental Epigenetics, 2018, 1–13 / Emma L. Marczylo, Miriam N. Jacobs and Timothy W. Gant ; Environmentally induced epigenetic toxicity: potential public health concerns Critical Reviews In Toxicology, 2016 VOL. 46, NO. 8, 676–700) / Sanne D. van Otterdijk and Karin B. Michels; Transgenerational epigenetic inheritance in mammals: how good is the evidence? The FASEB Journal article fj.201500083. Published online April 1, 2016. **Proposed change (if any):** **Multigenerational inheritance (or transmission)** : Following *in utero* exposure via the treated expectant female (F0), "multigenerational" phenotypes are those derived from direct exposure of the unborn children (F1) and their germ cells and/or gametes to the drug and expressed in the direct offspring (F1) and/or their direct descendant (F2) while not further expressed in the next generations. Following preconception exposure of germlines in males or of non-pregnant females (F0), multigenerational transmission/inheritance is defined by the observation of a phenotype in the direct offspring (F1) that is not transmitted to further generations. **Transgenerational inheritance (or transmission)**: Following *in utero* exposure via the treated expectant female (F0), "transgenerational" phenotypes are those, that can be observed in the direct first (F1), in the second (F2) and in the third offspring generation (F3) as a result of germline-mediated inheritance of (epi)genetic information, while the third (F3) generation has not been exposed to the drug. Transmission to further generations is meant to be observed too. Following preconception exposure of germlines in males or of non-pregnant females (F0), transgenerational transmission/inheritance is defined by the observation of a phenotype in the second offspring generation (F2) because this F2 generation has not been exposed to the drug	

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		but has inherited (epi)genetic changes that had occurred in the germlines of the exposed F0 generation.	
258		**Comment**: « Teratogen » definition means « A medicine or other environmental factor that can cause congenital **abnormalities** ». Whereas, births defects mean teratogenicity (line 142 p.5) and congenital anomalies mean birth defects (line 245 p.8), thus means teratogenicity. It seems not correct since « congenital abnormality » is a subcategory of congenital anomaly (the « congenital anomaly » definition includes « congenital abnormalities »). **Proposed change (if any):** « Teratogen » definition to be revised by « a medicine or other environmental factor that can cause congenital **anomalies** ».	
258		**Comment**: Suggestion to add lifestyle factors to include factors like alcohol. **Proposed change (if any):** ***Teratogen***: A medicine or other environmental **or lifestyle** factor that can cause congenital abnormalities.	
259-263		**Comment**: Clarify birth defects include both major and minor congenital malformations – the latter (minor) is more difficult to identify: in several cases, these anomalies become imperceptible during development of the child; the definition should be more complete, e.g. according to EUROCAT and Weston et al. (2016), mCM are a structural anomaly or dysmorphic feature observable at least at birth which does not impair viability or require intervention or treatment. **Proposed change (if any):** Recommendation to replace Minor and Major anomalies instead of Minor and Major congenital malformations and to take EUROCAT definition for Minor congenital malformation.	
286-289		**Comment:** For products with anticipated use in women of childbearing potential there is a need to reflect the current understanding of safety in pregnancy and/or breastfeeding in the summary	

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		of the safety specifications in the RMP as follows: relevant knowledge gaps regarding risks associated with the use in pregnancy and/or breastfeeding should be included as missing information. Therefore, this instruction would be confusing; so, we would propose to add more specificity or clarification. Given that most products will have little or no clinical data in pregnant women at the time of marketing authorization, as EMA has noted in the guidance, it would seem that there will be no established safety profile in pregnant or breastfeeding women. Therefore, the request to outline 'relevant knowledge gaps' seems confusing, as the safety profile as a whole would be the gap (and the missing information).	
277		**Comment**: According to GVP module V, "excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. "on-label". Please clarify that pregnant and breastfeeding women should only be included as missing information when they are not considered off-label. **Proposed change (if any):** Please consider adding the following sentence: 'This statement is applicable to pregnant and breastfeeding women, when they are not considered as an off-label population, as they are rarely included in clinical trials.'	
Line 277-312		**Comment**: Considering that the RMP Requirements for the applicant/marketing authorisation holder in the EU differ depending on the marketing authorization application and type of product, it would be appreciated if more guidance is provided in terms of the level of information to be included per RMP and per product type (e.g. full MA application, Generic product etc.). This is of high relevance having in mind the maturity of the product and the available data evidence in the areas of pregnancy and breastfeeding.	

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Lines 280-292		**Comment:** GVP Module V states that "if the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information in the RMP". Additionally, in the line 288 it is stated that "relevant knowledge gaps regarding risks associated with the use in pregnancy and/or breastfeeding should be included as missing information". It is not clear if this philosophy should be applied only if the MAH expects a different safety profile when treatment is used in pregnancy/breastfeeding or if safety during pregnancy/breastfeeding be should considered in general regardless of a difference in safety profile to the treated population. The latter would imply that most products would have safety in pregnancy/during breastfeeding as missing information. **Proposed change (if any):** Please provide clarification/specific information on the application context. Proposed change (if any): Additional text line 285: However, when use in pregnant or breastfeeding women is not recommended or contraindicated in the SmPc, it can be concluded that use in this population is not expected and there is usually no requirement to include these populations in the RMP as missing information	
286		**Comment:** It would be helpful to have clarification of the definition of products with anticipated use in women of childbearing potential. For example, does this wording cover all products, which may be used in this population, or just those used to treat chronic conditions or acute conditions commonly seen in pregnancy. The Guidance as it is, without additional clarification, could result in significant amount of additional work for diseases rarely seen/products rarely used in pregnant women.	

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291		**Comment:** Same Chemical class is to be considered as well **Proposed change (if any):** "products from the same **chemical or** pharmacological class"	
292-295, 412-415, 420		**Comment:** Not all types of risk minimisation measures do lead to recognition of safety concerns in the summary of safety specifications. To avoid ambiguities, we would advise it is clarified that this sentence refers to additional risk minimisation measures. **Proposed change (if any):** "For all three categories of safety concerns, recognition in the summary of safety specifications usually implies that additional pharmacovigilance activities for data collection and/or **additional** risk minimisation measures may be needed (see GVP Modules V and XVI)." Specific examples would include but not necessarily be limited to; **Patient/Adverse pregnancy outcomes** (disease course during pregnancy, completed pregnancy, pregnancy/delivery-related complications, elective or spontaneous abortion, preterm labor/delivery, ectopic or molar pregnancy, fetal death/still birth with or without fetal abnormalities, placental abnormalities, mode of delivery) as well as **Fetal/Neonatal/Child (F/N/C) Outcomes** (Congenital anomalies, delivery complications, pre/post term birth, delays in growth & development, impact related to side effects of drug exposure of pregnant woman, hospitalizations, infant drug withdrawal)	
Lines 296-299		**Comment:** The message conveyed in the part "contraception and the complexities of changing treatment if use during pregnancy is to be avoided" is not clear. **Proposed change (if any):** Please clarify part of the sentence "…contraception and the complexities of changing treatment if use during pregnancy is to be avoided."	

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Lines 296–299		**Comment**: With the introduction of GVP V Rev 2 and the RMP becoming a more streamlined document focusing on the identification, characterisation and minimisation of a product's important risks, it is not clear where such discussions (as outlined in Lines 296-299) should be included. Clarity in reference to the RMP would be beneficial, particularly: SIV.I would indicate whether or not these populations are to be included as missing information and SIV.3 would provide any exposure data in these populations. Therefore, is it anticipated this discussion would be included in SVII.3.2 under 'population in need of further characterisation' or 'anticipated risk/consequence of the missing information' or in SVII.I for an initial RMP? **Proposed change (if any):** Please clarify where in the RMP template this general discussion on pregnancy and breastfeeding should be included.	
Lines 300–307		**Comment**: This text indicates that background rates of adverse pregnancy outcomes, eg. in patients with diabetes, may need to be specified in the RMP S.IV, "Populations not studied in clinical trials". However, SIV.I would indicate whether or not these populations are to be included as missing information and SIV.3 would provide any exposure data in these populations. Clarification is requested regarding where, information such as background rates of adverse pregnancy outcomes, should be documented. **Proposed change (if any):** Please provide guidance where such information as background rates of adverse pregnancy outcomes should be documented within the RMP.	
Lines 300-307		**Comment:** The potential polypharmacy in patients with chronic underlaying conditions could affect the proper causality assessment and subsequent rates of adverse pregnancy outcomes.	

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		Proposed change (if any): Please consider the presence of polypharmacy as a limiting factor for the adequate provision of rates of adverse pregnancy outcomes in women with specific underlaying conditions.	
Lines 308-309		**Comment**: The phrase "related products" is unclear. **Proposed change (if any):** "Potential risks should be assessed based on findings from standard non-clinical studies, clinical data and epidemiological data on the **medicinal products of the same class and/or containing the same APIs**"	
Lines 309-310		**Comment**: If this text pertains to the RMP, it is suggested that 'adverse events of special interest' be replaced with 'safety concerns' as only important risks and missing information are included in the RMP and not all adverse events of special interest. **Proposed change (if any):** "This evaluation should inform what, if any, further studies and analyses are needed for the **safety concerns** ~~adverse events of special interest~~ as well as for any associated risk minimisation measures (RMM) to be implemented."	
Line 313 and Lines 315-319		**Comment:** Guidance is requested regarding the period for which the development of the child, after birth, should be followed. Also, it would be beneficial that the GVP suggest MAH **may** have specific guidance about pregnancy cases follow-up strategy to be used, adapted to the pregnancy course specificities and product particularities. **Proposed change (if any):** Please be more specific and determine the period of time for which the development of the child should be followed up after birth. Or provide a reference of a	

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		guideline which describes the information. Insert wording to suggest MAH **may** have specific guidance about pregnancy cases follow up strategy adapted to the pregnancy course specificities/steps and product particularities.	
314		**Comment:** The sentence states that 'spontaneous reporting during the post-authorisation phase is one primary source of information on adverse reactions'. Given the limitations of spontaneous reporting system, under-reporting will likely occur especially for those non severe conditions, thus it may not be the primary source. **Proposed change (if any):** Spontaneous reporting during the post-authorisation phase is ***one of the*** primary source….	
314-315		**Comment:** Spontaneous reporting rates of pregnant / lactating women are relatively low. More information is likely received from organized data collection schemes (e.g., national pregnancy registries). In addition, the collection of data from pregnant / lactating women where no AEs are observed would provide contextualizing information, but these instances are unlikely to be re reported by HCPs if there is not an accompanying AE. **Proposed Change (If any):** Spontaneous reporting, **together with organized data collection schemes such as national pregnancy registries** during the post-authorisation phase ~~is one~~ **are the** primary source**s** of information on **the uses of products during pregnancy and of** adverse reactions occurring following exposure in utero or during breastfeeding	
314-319		**Comment:**	

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		Regarding the requirement to follow-up with respect to the development of exposed children, it is also stated in lines 165-168 that some adverse pregnancy outcomes may only become apparent long after exposure has occurred, and should be accounted for in any evaluation or study design. Combined this implies that EMA expects MAHs to follow-up indefinitely, which may be a challenge for both MAHs and Reporters to continue to comply in the longer term. **Proposed change (if any):** Perhaps rephrase to "...should be followed-up to the extent possible in order to collect information on the outcome of the pregnancy and the development of the child after birth in accordance with the Risk Management Plan."	
320-325		**Comment:** This paragraph states that MAHs must collect and provide as many elements as possible for all cases irrespective of whether or not a product is authorized in use in pregnancy or breastfeeding. This is in contrast with note #7 on page 11 which instead indicates that exposure for product that are NOT authorized for use in pregnancy must be reported in PSUR.	
320-325		**Comment**: This paragraph makes clear reference to exposure during pregnancy and breastfeeding. However, Appendix 1 speaks only about EDP. **Proposed change (if any):** Recommend to specify in an additional appendix what must be done for breastfeeding.	
329-339		**Comment**: The MedDRA term **'exposure in utero'** does not seem to exist (cf: "use the MedDRA term 'exposure in utero' in the Reaction/event section") and the PTs usually used are the ones indicated in yellow below	

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331-332		**Comment:** Because of the increasing interest regarding multigenerational and transgenerational inheritance/transmission, specific MedDRA PT codes should be requested to MSSO to enable coding corresponding to events observed (i) in greatgrandchildren of a treated pregnant woman or in grandchildren of males and non-pregnant females (transgenerational) or (ii) in grandchildren of a treated pregnant woman or in children of males and non-pregnant females (multigenerational).	
333-335		**Comment** For foetal cases, it is indicated to use the MedDRA term 'exposure in utero' which is different from the recommendation made in the last version of MedDRA PTC v.22.1 (Sept. 2019), that indicates to use "Maternal exposure during pregnancy" or "Paternal drug exposure before pregnancy". Recommend to make the wording more generic – see in red **Proposed Change (if any):** For the route of administration, code, in the case of exposure in pregnancy leading to pregnancy loss or other adverse pregnancy outcomes, the route of administration as 'transplacental' and use the most appropriate MedDRA term indicating the exposure ~~'exposure in utero'~~ in the Reaction/event section;	
Line 340		**Comment**	

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		Concerning the ambiguity for coding pregnancy outcome, is it possible to provide a consensual principal for this issue; for e.g. resolved if the patient was born alive without harm, fatal in case of stillbirth, unknown if we don't have the information and avoid the use of not applicable or not resolved	
For lines 340-345:		**Comment:** While recognizing the importance of collecting long term appearance information for adverse health outcomes after exposure, the limitations in the process need to be recognized, as this not only includes the participation of MAH´s, but participation from the patients and healthcare professionals. **Proposed change (if any):** "Coding outcomes of exposure during pregnancy is open to ambiguity as a record of 'exposure during pregnancy, resolved' may mean that there is a prospective report of pregnancy exposure and either exposure discontinued, or the pregnancy has ended. Without reporting any further information regarding the pregnancy outcome this is not helpful. Efforts must be made to report the pregnancy outcome to the extent possible, even if this is not known until long after the exposure occurred and irrespective of whether or not the exposure was discontinued during the pregnancy	
341		**Comment:** The term "prospective" is introduced here for the first time while the definition of this term is only provided later (lines 353-362). **Proposed change (if any):** Consider adding a definition of prospective or alternatively move this section after the definition.	

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343-345		**Comment:** Similar comment to that raised regarding 314-319, "Efforts must be made to report the pregnancy outcome, even if this is not known until long after the exposure occurred…". **Proposed change (if any):** Perhaps rephrase to "... In accordance with the Risk Management Plan, effort may be required to report the pregnancy outcome, even if this is not known until long after the exposure occurred..."	
346		**Comment**: This statement applies to any neonatal/infant concomitant medication. Therefore, it is difficult to understand in this context. **Proposed change (if any):** Suggest bringing examples to elucidate the situation.	
Line 348		**Comment**: What does "potential harm" correspond to? is there a related definition? Do we need to understand that it corresponds to potential AEs? Does this cover for medication errors, misuses and remaining special situations without any AEs? Or is it potential harm in relation to Off label use? Precision should be given. **Proposed change (if any):** Please provide clarification what potential harm means.	
Lines 368-373		**Comment:** The text "Information on the exposure to other teratogens (e.g. Infections, occupational exposures)" gives the impression that all drugs are teratogenic. **Proposed change (if any):** "Information on the exposure to **teratogenic non-medicinal substances and medical conditions** ~~other teratogens (e.g. infections, occupational exposures)~~ and on other potential causes…".	
369		**Comment:** It is more appropriate to say risk factors rather than causes.	

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		Proposed change (if any): change from"…on other potential causes for the adverse pregnancy" to … "on other potential ***risk factors*** for the adverse pregnancy to.."	
370		**Comment:** Not only family history of congenital malformations in the mother should be collected but also her family history of neurologic and psychiatric diseases because this may be confounding factors of neurodevelopmental disorders (neurological or psychiatric) that may remotely be unravelled at school or preschool ages in her offspring. Similarly, the whole medical history including that of personal and family congenital malformation and of neurodevelopmental disorders in the father should also be collected.	
Line 379		**Comment:** Need to have the same requirements for exposure through breast feeding **Proposed change (if any):** Produce the same level of guidance for breast feeding exposure.	
Line 379		**Comment:** Header of table for 1st situation is not clear enough. **Proposed change (if any):** Please replace the Header for 1st situation as follows: Adverse Reaction in Mother and	
Line 379		**Comment:** Table P III.1 should be corrected according to Annex 2 of the CHMP Guideline on the exposure to Medicinal products during Pregnancy **Proposed change (if any):** Table P III.1 should be corrected according to Guideline	

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379		**Comment**: Table P III.1: situation where no adverse reaction in mother and no reaction in child occur, "No cases" is reported. The wording "No case" can be misleading even with the note 7. **Proposed change (if any):** No case **for ICSR reporting**[7]	
Line 379 Table P.III.1		**Comment**: Particular situation of Twins: The table indicates to create one case for each twin with an adverse reactions. How many maternal cases should be created? Just one coding "twin pregnancy" instruction is given to create 2 cases but what should be done if there is no AE? What should be coded in the mother? **Proposed change (if any)**: add instruction for this particular case	
Table P.III.1		**Comment**: The titles within the table are truncated, please address	
Line 379 (Table P III.1)		**Comment**: How is premature birth addressed? Is it covered by *adverse reaction in baby*? Same question for abnormal labour progression, e.g. prolonged labour, precipitous labour; it is presumably covered by *adverse reaction in mother*, but please consider more specific information or adding a footnote.	
Line 379 and Table P III.1		**Comment**: The requirements for the submission of individual case safety reports with pregnancy exposure is confusing. The title relates to expedited reporting requirements but the entries reflect creation of individual cases (not all of which may be reportable e.g. ADR in mother and no reaction in baby). The entry in relation to 'No adverse reaction in the mother' and 'No adverse reaction in the child' is also ambiguous since it states 'No case' but the footnote 7 clarifies that exposure cases should be reported in PSURs. Additionally, GVP Module VI also requires collection of such exposure cases. **Proposed change (if any):** Please clarify in the guideline when it is describing expedited reporting requirements versus requirements for individual case collection/creation.	

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Line 379 and Table P III.1		**Comment**: Could requirements for submission/creation of ICSRs with paternal exposure and breastfeeding also be included in the guideline? **Proposed change (if any):** Include tables for both paternal and breastfeeding exposure.	
Line 379 Table P III.1		**Comment**: Twins are the most common multiple gestation pregnancies. However, higher order gestations should also be considered. **Proposed change (if any):** ~~Twins~~ should be replaced by "**multiples**" to represent considerations for triplets, quads, etc.	
Lines: 386-389		**Comment**: Please consider adding observation during pre-authorisation phase (e.g. clinical studies) to be summarised in PSUR, together with all the other sources, already mentioned (spontaneous reporting, literature, etc.)	
386-389 and 396-403		**Comment**: The MAH monitors pregnancy/breastfeeding data as a part of routine surveillance. Although the draft guidance suggests presenting this information in 'Signal and risk evaluation', for products that do not have these topics as a safety concerns, inclusion of this data in said section seems conflicting with previous guidances. A summary of spontaneous ICSRs may not be value-added for all products (i.e., the drug is contraindicated in pregnancy or less commonly used for a drug class (e.g., oncolytics)). **Proposed change (if any):** The MAH would recommend that the totality of the available evidence during reporting period, including spontaneous data from post-authorisation sources, literature, and PASS studies, be reviewed and summarised in the PSUR-PBRER, only when a signal or new safety concern for this population arise.	
Lines 396-403		**Comment:** The guidance wording encourages the inclusion of information on pregnancy outcomes, even when this information is not specified as a safety concern or defined as important risk/missing	

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		information for a given product. Apparently, is also expected for this information to be presented in the signal and risk evaluation section on the PSUR. This might create ambiguity whether or not the evaluated information constitutes a risk or a signal, especially for products with an expected high rate of reports of unintended pregnancies (e.g. contraceptives) without any concerns regarding safety. **Proposed change (if any):** Please provide additional specific guideline on the proper use of the PSUR template and potential sub headers.	
Lines 404–405		**Comment:** As the access to information on observational studies sponsored by other MAH´s is limited, we recommend specifying the scope or the proposed analysis only to the studies under responsibility/sponsorship of the MAH. **Proposed change (if any):** "Data coming from an ongoing or finalised observational study (sponsored by the Marketing Authorisation Holder), e.g. a pregnancy registry, should be analysed a per…"	
409		**Comment**: P.III.B.4. Post-authorisation safety studies section describes several study designs, however there is minimal to no acknowledgement of the strengths and limitations of these study designs. **Proposed change (if any):** Suggest to acknowledge that the strengths and limitations of the different study designs have been published in other references. These strengths and limitations should to be considered when determining the most feasible study design to answer the pregnancy research question.	

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412-419		**Comment**: This section is titled 'Post authorisation safety studies' and indicates that where additional PV activities are warranted, PASS may be the appropriate tool. As PASS is a sub-set of additional PV activities we propose that the heading of this section is changed. Please also consider providing examples of additional PV activities that are not PASS. It is noted that pregnancy registries are defined as PASS (row 419), however such registries may not always be a PASS. **Proposed change (if any):** • Re-title the section heading to '**Additional Pharmacovigilance Activities'** • Additional text (line 419): **Alternative tools for additional pharmacovigilance include <<insert examples>>.**	
416-419		**Comment**: This section on PASS provides some suggestions for study designs and refers to the epidemiological section of the guidance for more information. PASS may, however, not always be epidemiology studies and several study types are described in GVP VIII and we propose that these should be referenced; e.g. non-clinical, pharmacokinetic (see P.III.B.4.21), interventional or non-interventional (see P.III.B.4.2.). Later in the document available date sources in the EU are described (P.III.C.2.). We propose these are also included as a reference in the PASS section. **Proposed change (if any):** Current text: ~~**A PASS may constitute a drug utilisation study or it may investigate specific risks to the embryo, foetus or child. Potential study designs for the latter include all epidemiological designs in principle, including but not limited to pregnancy registries (see P.III.B.4.2.1.).**~~ New text: **A PASS may constitute a drug utilisation study or it may investigate specific risks to the embryo, foetus or child. Potential study designs for the latter include all epidemiological designs in principle, including but not limited to**	

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		pregnancy registries (see P.III.B.4.2.1.). A number of data sources are available in the EU for carrying out drug utilisation studies and other non-interventional PASS (see P.III.C.2.). PASS may also be non-clinical, pharmacokinetic (see P.III.B.4.1) or interventional.	
416-417 v. 439-445, 477-480		**Comment**: This paragraph in P.III.B.4 indicates "PASS may constitute a drug utilisation study or it may investigate specific risks to the embryo, foetus or child…", which is not consistent with a later section that states "If a PASS is considered warranted, … The evaluation should consider all relevant outcomes throughout the human developmental lifecycle." The drug utilization study that does not carry on any evaluation of outcomes/endpoints should be mentioned in the later section to clarify if drug utilization alone can serve as a PASS (or not). Further, it is unclear at what circumstance that MAH should conduct drug utilization study for a new product of unknown likelihood of being prescribed to pregnancy women. Please clarify a timing frame to put into perspective. Guidance is requested from EMA on overcoming the practical challenges of PASS studies due to requisite long durations, small sample sizes, limited availability and beneficial value. **Proposed change (if any): ..** If a PASS is considered warranted, … The evaluation may include to study the pattern of use or consider all relevant outcomes throughout the human developmental lifecycle.	
417		**Comment**: Specific drug related risks may also apply to the pregnant woman/mother – not only to the foetus/child. **Proposed change (if any):** Suggest including "pregnant women" in the sentence "specific risks to the embryo, foetus or child".	

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421 - 426		**Comment**: The statement "Considerations regarding risk proportionality etc. does not necessarily apply to the decision about whether or not to perform a PASS, and therefore may not belong to this section. **Proposed change (if any)**: Suggest deleting text or as an alternative moving it to the Risk minimisation measures section (B7).	
Lines 423-426		**Comment**: It is not clear what the section aims at conveying and what is the guidance behind it. **Proposed change (if any)**: Suggest removing or reword language with more clarity.	
Lines 427-438, second bullet (lines 432-433)		**Comment**: if outlined bullets are supposed to provide examples when the use of medicine in pregnancy or breastfeeding is expected, then the second bullet does not seem to represent such an example, i.e. if potential risk for the child has been suggested by pre-clinical data or characteristics of the medicine, then the medicine should be avoided rather than expected to be used. **Proposed change (if any):** Delete second bullet or revise lines 427-428 to focus on the situation where PASS will be of particular relevance.	
427-438		**Comment**: A PASS will only be conducted to address risks that are included in the RMP, and thus only 'important' risks. The second bullet, however, refers to potential risks without qualifying that it needs to be important. Given the context of the section we propose alternative text to avoid confusion with terminology. **Proposed change (if any):** • if a ~~potential~~ possible risk to the child has been suggested by non-clinical data, a signal (see P.III.B.5.) or based on the chemical or pharmacological properties of the medicine;	

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Lines 429-431		**Comment**: It is suggested that an example be included of the type of condition that might warrant continued treatment during pregnancy without this being considered as mandatory for that condition. **Proposed change (if any):** "when use of the product cannot be discontinued during pregnancy due to the disease being treated **(such as with epilepsy, a major depressive disorder, if appropriate)**, …"	
436		**Comment**: Recommendation to use "effectiveness of RMM **Proposed change (if any)**: if measuring **effectiveness of** ~~compliance with~~ RMM in place regarding pregnancy or breastfeeding (e.g. in the 436 product information, educational material or a pregnancy prevention programme) (see P.III.B.7.) 437 is needed.	
For lines 443-445		**Comment:** Guidance is requested for length of time to follow a newborn/infant/child who may have been exposed prenatally to study drug. Also guidance is requested from EMA on overcoming the practical challenges of PASS studies due to requisite long durations, small sample sizes, limited availability and beneficial value. While recognizing the importance of collecting long term appearance information for adverse health outcomes after exposure, the limitations in the process need to be recognized, as this not only includes the participation of MAH´s, but participation from the patients and healthcare professionals. **Proposed change (if any):** The child should be followed up to the extent possible to capture the relevant information on health or developmental impact.	

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Line 446-447		**Comment:** Current wording indicates that feasibility aspects should be considered in the study protocol phase. It should be stressed that feasibility aspects should also be considered prior to initiating a study, and a study should not be initiated unless drug utilization patterns indicate that the study is likely to be feasible. Additionally, time points for feasibility/futility assessments should be specified in the protocol. Clarification is also requested from EMA on if the aforementioned PASS study is referring to an interventional vs. observational trial.	
449		**Comment**: It is not clear whether this recommendation is only relevant where an indication for pregnancy is to be approved. This also include breastfeeding and likelihood of GI absorption, e.g. separation between small molecules and proteins. **Proposed change (if any):** Please clarify whether this recommendation is only relevant where an indication is to be approved.	
Lines 451-454		**Comment**: Where the impact of pregnancy on medicine plasma levels is based on the evaluation of pharmacokinetic (PK) studies this should be justified in the relevant regulatory submission such as a marketing authorisation application. **Proposed change (if any):** "If use of a medicine during pregnancy is indicated and from all available evidence, there is no suggestion of harm, it may be appropriate to evaluate the impact of pregnancy on medicine plasma levels in pharmacokinetic (PK) studies; sometimes, it is suggested that free rather than total medicine plasma levels are monitored in pregnant women. **Either of these approaches should be justified in the relevant regulatory submission.**"	
474, 486		**Comment**: Based on GVP V Rev.2 effectiveness evaluation is mainly measured for additional RMM. **Proposed change (if any)**:	

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		474 "Studies to evaluate the effectiveness and broader impact of **additional** RMM."486 "time with implementation of **additional** RMM in specific populations."	
480-482		**Comment**: It is difficult to understand how this request to exam the extent of use will arise. Given the concern of under reporting for any spontaneous cases, lack of relevant denominator will make it difficult to put the number of spontaneously reported suspected adverse reactions into perspective. Please elaborate.	
482		**Comment**: The data sources listed in the sentence may inform about what outcomes would be relevant in specific studies, but not about study/study design in general. **Proposed change (if any)**: Replace "studies" with "study outcomes" or similar.	
Lines 487-488		**Comment**: The statement that secondary data use with existing data sources is preferable for epidemiological studies in pregnancy/breastfeeding does not appear to align with prior lines 475-477, where the text advises that it may be appropriate to initiate a safety study at the time of marketing authorisation (i.e., when secondary data would not yet be available). It would be helpful to clarify the language on what is preferred. **Proposed change (if any):** Please clarify the language.	
487-489		**Comment**: agree with advantages of using existing data sources over prospective pregnancy registries but **the limitations must be underlined**, specifically the representativeness of the different EU regions, the lack of information about major confounding factors such as maternal alcohol intake / socio-economic status	
Line 489-491		**Comment**:	

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		"Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.III.A.1.3.), it is usually necessary to include participants from more than one country in order to achieve adequate power." **Proposed change (if any):** Suggest recognizing the situation in the guideline that when exposure to a medicine is extremely low, it is possible that including participants from multiple countries would still not be able to achieve adequate power.	
492		**Comment**: The well-known limitations to pregnancy registries (limited statistical power for specific risks such as specific major congenital malformations, challenges related to patient recruitment and retention etc) could be highlighted in this section. Also, a separate subsection for drug safety studies based on secondary data collection (similar to section 4.2.1 about pregnancy registries) would be desired to have included. **Proposed change (if any)**: Please consider to include the limitations to pregnancy studies as well as a subsection for drug safety studies.	
493-494		**Comment**: The guideline does not provide guidance on when and under what circumstance a pregnancy registry should be considered. **Proposed change (if any):** Guidelines or basic principles should be provided on when and under what circumstances a pregnancy registry should be considered. Suggest to also include specific examples for when a registry could be used.	
495		**Comment**: The first bullet in the Pregnancy registries section states, "Registries that, in principle, aim to capture all pregnancy women with the disease are generally more useful than medicinal product-specific registries…" In fact, given the challenges of enrolling pregnancy women, disease registries have not proven to overcome the challenges of specific product	

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		registry. Because the medication use is likely reflective of the usage of medication in real-world; for any novel medicine lacking safety data among pregnant women, they are less likely to be adapted by patients and prescribers, therefore any registry including disease registry will suffer the similar challenges of slow enrolment. **Proposed change (if any):** Suggest to state the above comment in this section	
495		**Comment:** Add "disease" registry for clarity **Proposed change (if any):** "**Disease r**egistries that…"	
501		**Comment:** The third bullet comments on facilitating the inclusion of comparator groups. Suggest to provide an additional comments on the criteria to use for selecting comparator groups, how and what types of comparator groups should be considered. **Proposed change (if any):** Suggest to incorporate the above comment into this section.	
504 - 509		**Comment:** This paragraph suggests the integration of public data source with primary data collection by the MAH as a desirable approach. Although in principle such a method may be pursued, barriers to achieve such a desirable integration are often faced. The most common ones are represented by the challenges for the MAH to access public data sources and by the complexity of establishing a study specific public-private governance. We propose the guidance acknowledges these challenges and limitations.	
504-509		**Comment:** Hybrid design registries are very challenging to set up because collaboration with academic teams/network – refer to comments made to the EMA Registry position paper.	
512-515		**Comment:** Retrospective cases may have a concern of recall bias. It is true that such cases are still of value, but they may have to be analysed separately from the prospective cases.	

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516-520 and 537-541		**Comment**: These two paragraphs relate to long-term evaluation of neonates or infant for development maturation. In both instances the text refers to "follow up", implying a prospective approach in this sort of studies. However, we propose acknowledging the advantages of a retrospective approach as a more feasible and efficient option for long term studies.	
519-520		**Comment:** It may not be feasible to establish long term follow up in any pregnancy registry, due to the reasons: 1) rare outcomes that require large sample size, 2) loss -to-follow up is much higher and 3) unknown confounding factors that should be collected. Despite the challenge, it may be worthwhile to consider hybrid approach by linking different existing data source. Additional description on control/comparator groups within guidance is requested (e.g. see line 554 below).	
527		**Comment**: The intentions in the text are well taken, however it would be helpful with a few examples to clarify. **Proposed changes (if any):** Please consider to add example on the assessment of long-term pregnancy outcomes.	
527		**Comment**: With regards to long-term pregnancy outcomes, in the context of increasing interest in multigenerational and transgenerational transmission, depending on the mechanism of action and on relevant literature or preclinical toxicology studies, one should consider adding the possible recommendation of collecting outcomes of or data on subsequent offsprings of a child that would have been exposed in utero.	

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Lines 533-536		**Comment:** What reference from a guideline describes what measurements should be used at different ages? **Proposed change (if any):** Please provide reference for guideline which describes what measurements should be used at different ages.	
For lines 537-538		**Comment:** While recognizing the importance of collecting long term appearance information for adverse health outcomes after exposure, the limitations in the process need to be recognized, as this not only includes the participation of MAH´s, but participation from the patients and healthcare professionals. **Proposed change (if any):** Depending on the outcome of interest, reasonable follow-up efforts may be into preschool or school age, and/or adolescence, as appropriate to reflect the neurodevelopmental outcomes mentioned.	
537-541		**Comment:** About hybrid design, same comment as for pregnancy registries: operational setup is very challenging, the EMA should facilitate the framework with pilot projects. Refer to comments made to the EMA Registry position paper.	
554		**Comment:** The control group, when part of the study, should best be made of untreated patients presenting the target disease of the product under evaluation. If not possible for ethical reasons, then a group made of a standard of care or of a relevant comparator can be considered. Refer to comments made to the EMA Registry position paper.	

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554-555		**Comment:** The statement states that "Attempts to minimise selection bias should be made for example by ensuring a population-based approach such as through national birth cohorts". But it is unclear what selection bias can be minimised by using population-based approach. **Proposed change (if any):** …using epidemiological approach, it is important to select comparable patients (not entire cohort) based on risk factor profiles. Or this statement refers to generalizability.	
568		**Comment**: Should this bullet explicitly include age post partum, for those endpoints which only become apparent with post natal developmental. Additional clarification is requested regarding the decision-making for which pregnancy outcome and outcomes of child should be evaluated. **Proposed change (if any):** which pregnancy outcomes and outcomes **and at what age** in the child will be evaluated	
568		**Comment:** States "which pregnancy outcomes and outcomes in the child will be evaluated", Suggest to add a comment on what efforts have been taken to validate the outcomes, including use of outcome algorithms cited in the literature. In addition, comments on what constitute a high-performing algorithm included (e.g., PPV, sensitivity, etc).	
572-573		**Comment**: Is "common" an appropriate term? The use of the medicinal product is based on the medical need of the mother and not on the basis that she is breastfeeding. **Proposed change (if any)**:	

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		In cases where no human data are available on the extent of medicine transfer into breast milk, where use by breastfeeding women is ~~expected to be common~~ **difficult or unable to be avoided, due to the medical needs of the mother……**	
584-587		**Proposed change (if any):** So far, PASS in breastfed children are very rare. However, in the case of a medicine **where use in lactating women is difficult or not possible due to the medical needs of the mother,** ~~highly used in women who could breastfeed,~~ with an unknown potential for serious adverse reactions in breastfed children, establishing safety information in the post-authorisation phase should be considered as an important source of information	
588-591		**Comment:** "Pregnancy registries in which new-borns are further observed could include the collection of information on breastfeeding to allow a comparison of a group of breastfed children to those not breastfed and those breastfed in mothers who are not treated with the product of interest …" It is unclear about the purpose of the PASS in breastfed children is hypothesis generating or testing. Lacking pre-specified outcome of interest pregnancy registry has limited the value, because all data is collected via pre-populated questionnaires. The comparison between breastfed and non-breastfed children won't be adjusted for any risk factors, if not collected already.	
594 Signal management		**Comment**: With regards to signal management, there is increasing interest in multigenerational and transgenerational inheritance/transmission of phenotypes owing to in utero exposure. This is extending the concept of "not visible anomalies" at birth while still being congenital anomalies. Means and tools to assess such theoretical/potential signals/risks should be implemented. For example, to start with, appropriate MedDRA terms need to be created to help retrieving cases in PV databases. Linkage between grandparents and/or great-grandparents should be rendered	

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		possible when assessing a child case. As a mirror image, regarding in utero exposure, data collection could be extended to next generations for medicines for which there are hints for multigenerational or transgenerational transmission of some phenotypes.	
Line 594 P.III.B.5. Signal management		**Comment:** The whole paragraph is talking about adverse pregnancy outcomes. What about breastfeeding issues?	
595-598		**Comment:** How will signals related to pregnancy and pregnancy outcomes be handled in EVDAS, considering competing endpoints, very low incidence of individual birth defects, and multiple prevalence categories (live birth rate, birth rate and total prevalence)?	
Line 596		**Comment**: Signal detection activities are not limited to Adverse reactions spontaneously reported but include any source of data. **Proposed change (if any):** the challenges for the other source of safety data should be addressed as well	
Lines 609-610		**Comment:** While recognizing the importance of collecting long term appearance information for adverse health outcomes after exposure, the limitations in the process need to be recognized, as this not only includes the participation of MAH´s, but participation from the patients and healthcare professionals. **Proposed change (if any):**	

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		In this phase of signal detection and verification, reasonable efforts should be made to confirm detailed information (e.g. timing of gestation, duration, product) regarding exposure during pregnancy	
631-634		**Comment:** This type of activity may have consequences for AE reporting and this should be noted here in line with section VI.b.1.1.4 of GVP Module VI and lessons from the IMI WEB-RADR project. **Proposed change (if any)**: Clarify AE reporting requirements associated with this type of monitoring activity in accordance with GVP Module VI	
Lines 635 – 639		**Comment**: Clarification of agency's expectations is needed. **Proposed change (if any):** We recommend the agency be more specific and provide examples regarding the expectations of the RMMs implementation and the type of tools provided to the HCPs.	
640-660		**Comment**: There is a mix of quite detailed information that may be relevant to the prescriber, or to the patient but insufficient communication if only in the PL. **Proposed change (if any)**: Suggest adding HCP or Patient-specific specific educational materials.	
649-654		**Comment:** An overview of the risks to the pregnancy of the untreated condition should also be included in the guidance. Additionally, the difficulty in assessing for individual malformations should be recognized and that it is possible that only aggregate data can be used.	

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Lines 662-665		**Comment**: This statement is ambiguous and as well as communication for patients/carers differing from that for healthcare professionals, it could imply that the communication be tailored according to the specific healthcare professional. **Proposed change (if any)**: "Communication should be tailored for addressing women/adolescent female patients and their partners, as well as parents or carers in the case of adolescent female patients, and healthcare professionals (including in particular general practitioners, paediatricians, obstetricians and gynaecologists, midwives, nurses and pharmacists). **Note: This does not imply that communication should differ depending on the specific healthcare professional.**"	
666		**Comment**: As part of the RMMs, consider the theoretical/potential (epi)genetic effects of the drug on oocytes (post natal) or on germ cells (in utero)	
Lines 666-694		**Comment**: Please consider adding a bullet related to the risk of withdrawal symptoms. **Proposed change (if any):** Where a risk of withdrawal symptoms in neonate is expected, based on pharmacological characteristics of the medicine, minimising exposure toward the end of pregnancy.	
Lines 667-694		**Comment**: One very common form of routine risk minimisation related to pregnancy/breastfeeding is general SmPC wording about not administering the product to the mother unless the potential benefits outweigh the potential risks to the foetus/baby. This is usually based on an absence of evidence. What is the GVP position on the use of such wording going forward?	

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		Proposed change (if any): Provide guidance on routine risk minimisation related to SmPC wording about not administering the product to the mother unless the potential benefits outweigh the potential risks to the foetus/baby.	
From line 674 to line 676		**Comment**: mitigating the risk in the event of unplanned pregnancy could also include, as mentioned in introduction, to avoid teratogenic chronic treatment initiation, as far as possible, at the very young age (young female children).	
680-682		**Comment**: In addition to the risk of transmission via semen, please consider the risk of transmission via the spermatozoa themselves, i.e. in the context of (epi)genetic changes in the DNA.	
685		**Comment:** Requests that EMA clarifies language regarding the decision maker. **Suggested change (if any)**: "If the decision **by the patient in consultation of the HCP** is taken to breastfeed whilst continuing maternal medicine intake and there is a (potential) risk for the child, the infant should be carefully monitored and breastfeeding discontinued in the case of the adverse signs and symptoms;"	
Lines 692 – 694		**Comment**: Please clarify. **Proposed change (if any):** Under RMMs, we recommend that EMA clarify the expectation for patients in reference to Line 693 "information available supporting them making informed decisions regarding the most appropriate choice in the individual case".	
698		**Proposed changed:** if there are important identified or potential risks **or missing information** and routine RMM is not considered sufficient.	

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Lines 722-740		**Comment:** While recognizing the importance of provide meaningful information to facilitate the selection of an appropriate contraceptive method, the responsibility of an individual informed choice goes beyond the MAH product information, as HCPs and patients themselves have a critical role in the process. **Proposed change (if any):** Please consider the inclusion of additional information regarding the roles and responsibilities of the respective members of the healthcare chain on the topic.	
Lines 722-740		**Comment**: Please consider adding an information on drug-drug interaction that can impact effectiveness of contraception. **Proposed change (if any):** Caution should be taken in case of concomitant use of medications that can interfere with contraceptive methods, e.g. medication with a known pharmacokinetic or pharmacodynamic interactions with contraceptives.	
Lines 734-737		**Comment**: For more precision, recommend changing "half-life of the product" to "Elimination half-life" in Lines 734-737 and throughout the guideline. Suggest additional discussion on the maternal needs for treatment (ie disease prognosis and limited treatment options) before providing specification that pregnancy must be exclusion criteria. **Proposed change (if any):** "Instructions should specify that pregnancy must be excluded before treatment initiation and each repeat prescription and for how long pregnancy must be avoided, taking into account the **elimination half-life** ~~half-life of the product~~ and/or its metabolites, the pharmacological effect, and for some genotoxic products, spermatogenesis and/or folliculogenesis."	
From line 734 to line 737		**Comment:** it is stated that Instructions should specify that pregnancy must be excluded before treatment initiation and each repeat prescription and for how long pregnancy must be avoided,	

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		taking into account the half-life of the product and/or its metabolites,(..). However, in this sentence, product should be modified by active substances (since product should include active substance and metabolites)	
738-743		**Comment:** Clarification is requested if this is a recommendation or an instruction	
From line 744 to line 745		**Comment:** For readability reasons, the sentence "scenarios when a PPP may be needed include chronic conditions where treatment may be started long before the patient becomes of child-bearing potential or is considering pregnancy" could be modified as follows: "Chronic conditions where teratogenic treatment may be started long before the patient becomes of child-bearing potential or is considering pregnancy should also be taken into account in PPP."	
Line 759		**Comment:** This section does not address as per similar GVP Module and GVP structure (see latest issued GVP IV module on paediatric population), the role of MAH/applicant, EMA, PRAC, RMP, PSURs, Signal, etc…..these sections/topics for which there is guidance in Part B have no counterpart in Part C: is this because this is not relevant to this guidance or are missing information here. **Proposed change (if any)**: Please provide clarification.	
Lines 759-784		**Comment:** The proposed guideline will benefit of the inclusion of additional information on the roles and responsibilities of other members of the EU network, as it was already consistently presented in other GVP adopted modules. This will facilitate the communication, but also will help to align expectations for all the involved parties. **Proposed change (if any):** Please provide additional information about the roles and responsibilities of additional members of the EU network (e.g. HCP (including pharmacist´s), NCA´s, PRAC)	

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LINE 760 Section P.III.C.1 Submission of PSUR in the EU		**Comments:** To identify teratogenic products, should the MAH use the following guide: Drugs belonging to a class of substances having a similar chemical structure or mechanism of action that can be - Substances of which the teratogenic, embryotoxic, foetotoxic or mutagenic effects in humans is suspected from case reports and animal studies - Substances of which the potential for teratogenic or embryotoxic/foetotoxic or mutagenic effects in humans has already been established • Regarding table P.III.2 would it be possible to provide interval and cumulative only for drug therapies considered essential for maternal and/or fetal benefit and for products in which signal trends in pregnancy outcomes have been detected? For the other drug types, proposal would be to provide interval data only. • Suggest that the table include a Pregnancy Outcome for "Unknown Outcome" • Regarding sentence - Overall malformation rates & proportional prevalence of …. "have to be compared" and it is suggested to modify to "when this data is available and relevant". • Should this table be included in Section 16 of the PSUR or as an EU Regional Appendix ?	
761		**Comment:** Please specify if 2 tables should be included in the PSURs, one for cumulative data and one for reporting period interval data OR if 1 table with cumulative data will suffice. We believe flexibility in this regard is the most appropriate approach, edit proposed below. **Proposed change (if any):** For all teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the RMP or the PSUR, Table P.III.2. should be provided in the PSUR and filled in	

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		completely with reporting period interval and cumulative data. ***This can be provided as a single table with cumulative data or as two separate tables, one for cumulative data and one for reporting period interval data.***	
Lines 761-763		**Comment**: Suggest amending text requiring that the cumulative table should be provided upon request or if deemed important to present in the evaluation by the MAH. **Proposed change (if any):** "…For all teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the RMP or the PSUR, ~~P.III.2. should be provided in the PSUR and filled in completely with reporting period interval~~. **~~and~~ Cumulative data should be provided upon request or if deemed important to present in the evaluation by the MAH."**	
761-770		**Comment**: Content of section P.III.C.1. Submission of period safety update reports in the EU, including table P.III.2.: "Table for reporting numbers of individual case safety reports in periodic safety update reports", is more related to PSUR content so we would suggest this section is removed while its content is moved to section P.III.B.3. Periodic safety update report. **Proposed change (if any):** Move content of section P.III.C.1. from P.III.C to P.III.B.3. Periodic safety update report (can be added as last bullet after line 408).	
764-769		**Comment**: Pregnancy exposure data is typically not available with the exception of data collected within clinical studies. As a result, calculating the reporting rates may either represent a misleading estimate or not be possible.	
Line 770		**Comment**: Table P.III.2 includes a list of pregnancy outcomes (total of 8). Suggest allowing MAHs flexibility in providing list of pregnancy outcomes	

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		Proposed change (if any): Suggest allowing MAH's flexibility in providing the list of pregnancy outcomes.	
770		**Comment**: In "Table P.III.2.: Table for reporting numbers of individual case safety reports in periodic safety update reports": - Where should be entered **"Neonatal Disorders"** (cf : « *Additionally, any neonatal adverse reactions and functional anomalies need to be captured*. »)**?** - Should « **live birth » with « neonatal disorders** » be classified in Live birth without congenital anomaly » - Define **Neonatal disorders** in Terminology - Why only "**Withdrawal syndrome**" is described **Proposed change (if any)**: Update the table accordingly	
782-784		**Comment:** Contrary to what is written in lines 782-784, we found that GPV Module VIII for PASS states that study protocols and reports "should be posted on EU PAS", rather than "shall be posted on EU PAS". In that context, no differentiation appears to be made between imposed and non-imposed PASS, and also there is no obligation for either to be posted to the EU PAS Register. We found that, in module VIII, it states: "Non-interventional PASS should be registered in the EU PAS Register before the study commences or at the earliest possible date, for example if data collection had already started for a study included in the risk management plan. The study protocol should be uploaded as soon as possible after its finalisation and prior to the start of data collection. Updated study protocols in case of substantial amendments, progress reports and the final study report should also be entered in the register (as soon as possible and preferably within two weeks after their finalisation)." Thus the guidance in this document that there is an obligation to make study protocols and study reports of imposed PASS available in the EU PAS Register seems to be inconsistent with GVP Module VIII. Please clarify.	
784		**Comment**: clarify PASS – suggest adding "non-interventional" for completeness and to avoid any risk of confusion upon release. **Proposed change (if any):** From: for all imposed PASS (see GVP Module VIII) and encouraged for all other PASS.	

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		To: for all imposed non-interventional PASS (see GVP Module VIII) and encouraged for all other non-interventional PASS	
Line 786 App 1		**Comment**: It is suggested that this appendix not be copied from relevant CHMP guideline on exposure of medicines during pregnancy. This will avoid the possibility of this GVP becoming outdated if the CHMP is updated in future. A cross reference to the CHMP guideline is already provided (see line 95-96) therefore it is proposed that this appendix be deleted. **Proposed change (if any):** Remove paragraph (Lines 786-796).	
851		**Comment** : P.III. Appendix 1, section C on paternal exposure has no details regarding "Medical products exposure" as compared to maternal exposure. We would advise the following would be added: dosage, date of first use, date of end of treatment and duration.	
804-805		**Comment**: Information related to the address of the place where the patient wants to deliver, and the identification of the gynaecologist are considered as privacy data and will lead to issue for transmission due to GRPD. **Proposed change (if any):** include a section on the data privacy expectation.	
807		**Comment**: The word "patient" is confusing here, because although it should be understood by all as the "pregnant woman being treated with drug x", in case of congenital anomalies (pregnancy outcome), the patient is usually understood as the neonate or child when entered in PV databases. **Proposed changes (if any):** Identification of ~~**patient**~~ **the pregnant woman receiving the drug [x]**	

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Lines 810-816		**Comment**: Please consider adding question if the pregnancy is spontaneous or assisted.	
818-822		**Comment and proposed change**: Other must have information for study of NDD: Maternal socio-economic status or deprivation index or IQ or education level	
823		**Comment and proposed changed:** Addition information required such as pregnancy test and contraception used before pregnancy. Consider adding a section on the pregnancy prevention program with specific questions related to compliance on this program (increased interest of Health Authorities).	
Lines 823-842		**Comment:** Please consider adding question on information on medical/surgical interventions (e.g. foetal transfusion, amniocentesis, chorocentesis, fetoscopy, foetal surgery for spina bifida, myelomeningocele), performed to mother or foetus during pregnancy, if any, primary in the context of confounding factors.	
Line 824		**Comment:** The date of last menstrual period (LMP) is explained. To determine gestational age, the first day of the LMP needs to be used. **Proposed change (if any):** Replace text in line 824 with the following: First day of last menstrual period (LMP)	
Line 825-827		**Comment:** The wording for section P.III. Appendix I (Questionnaire), Line 825-827:" Gestational age at the time of the first contact with MAH", "Gestational age at the time of drug exposure…" are not	

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		consistent with section P.III.B.2. (Reporting of AE), Line 363:" Gestational age when the suspected Adverse Event was observed…" **Proposed change (if any):** To add a new line to the Questionnaire in P.III Appendix 1 as follows: "Gestational age at the time when suspected Adverse Event was observed"	
Line 831-836		**Comment:** In Section P.III. Appendix I (Questionnaire), to namely ask about contraceptive method used will reduce the need for potential follow-up question. **Proposed change (if any):** To add a new line to the Questionnaire in P.III Appendix 1 as follows: Contraceptive method used	
Lines 843-844		**Comment**: Recommend to include the date of delivery **Proposed change (if any):** "Delivery - **Date of delivery** - Mode of delivery"	
851		**Comment and proposed change:** Regarding paternal history, it may be worth repeating the request for personal and family history as in lines 847-850: • History of congenital abnormality, psychomotor retardation in the family (specify paternal/maternal and relationship). Consanguinity between parents (specify degree).	

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Lines 855-856		**Comment:** Recommend to include the dates of exposure to the product **Proposed change (if any):** "Medical products exposure **Dates of exposure to product** **D. NEONATAL INFORMATION"**	
Lines 887-902		**Comment:** Additionally, to the comments provided for Lines 722-740, the purpose and expected proper use of the information provided in P.III. appendix 2 need to be clarified with special focus in the context of communication, product label information and its interrelation with Pregnancy Prevention Programs **Proposed change (if any):** Please provide clarification/specific information on the application context.	
Lines 887-902 App 2		**Comment:** The definition/classification of "highly effective" contraception is not aligned with other available categorizations (e.g. CTFG guideline) that also include (as an example) combined hormonal contraception, progestogen only HCs associated with inhibition of ovulation and bilateral tubal occlusion. While it is understood that the differentiation in the table follows PI under "typical use", the terminology could be reviewed to clearly distinct the information provided by guidance's used in clinical development context versus the ones used in post marketing by introducing (as an example) the concept of "user dependency" rather than "effectiveness". This would help to avoid confusion or misunderstanding between the clinical development and post marketing application context. **Proposed change (if any):**	

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		Please review wording and categorization in P.III. Appendix 2.	
887		**Comment:** For P.III. Appendix 2: Pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential, sterilization of either partner is not included. Suggest that male and female sterilization be mentioned in text and/or included in table.	
889		**Comment:** "Teratogenic medicines" seems more aligned with the below stated "teratogenic prescription" and may have a different connotation than "medicines of teratogenic potential". Consider changing to "teratogenic medicines". **Proposed change (if any):** Pregnancy testing and contraception for pregnancy prevention during treatment with ***teratogenic*** medicines ~~***of teratogenic potential***~~.	
Line 898		**Comment:** concerning the risk of pregnancy at start of a new method of contraception, a repeat pregnancy test should be performed at 3 weeks. Time period between contraception initiation and teratogenic treatment initiation is lacking **Proposed change (if any):** In order to avoid pregnancy during first 3 weeks of treatment, proposal to mention that the contraception should be initiated 1 month before teratogenic treatment initiation	
902		**Comment:** Lines 908-909 state that Less effective methods are based on greater than 1% failure rate, while table (line 902) states these as effective methods. Proposal to align table with text as highly and less effective methods are both effective methods. Barrier methods and other effective methods	

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		of contraception should be incorporated within a listing that provides information and definitions related to women of childbearing potential and methods of contraception. **Proposed change (if any):** Add "less" in table in line 902 to say "**Less** ~~E~~effective methods".	

Please add more rows if needed.

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<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
ENTIS European Network of Teratology Information Services

Name of organisation or individual
[redacted] [redacted] the Israeli Teratology Information Service, Jerusalem, and the Hebrew university Hadassah Medical school

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	I would like to congratulate EMA for the comprehensive effort in trying to update the Guideline on good pharmacovigilance practices Population specific considerations III: Pregnant and breastfeeding women. However, we have reservations to the draft and feel that the clinical aspects of treating women in pregnancy and lactation should have been its focus.	

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 co*
110-112		Comment: The term foetal toxicity is more appropriate than teratogenicity for examples where the mechanism of action of the medicine is related to the mechanism foetal adverse reaction. The timing is the foetal rather than the embryonic period, and dose response is better demonstrated. With classic teratogenic effect, the relationship to the mechanism of action is often poor, timing is organogenesis, sometimes with threshold effect, rather than dose response. Proposed change (if any): Change teratogenicity to foetal toxicity and delete embryo/ from line 112.	
117-119		Comment: The risk via semen exposure in humans is mostly theoretical at this point, even with the medications carrying the highest teratogenic potential [see Scialli et al. (2015) Potential seminal transport of pharmaceuticals to the conceptus. 2015]. Proposed change (if any):	
121-122		Comment: Drug properties and animal studies are not mentioned. Proposed change (if any): Consider adding drug properties and animal data on transfer of medication to milk.	
147-150, 151		Comment: The organogenetic period, which is the period of maximal sensitivity to abnormal development as a result of teratogenic drug exposure, is defined from the beginning of the 3rd week till the end of the 8th week after fertilization, or gestational weeks 4-10 counting from the last menstrual period [See Moore et al. The Developing Human: Clinically Oriented Embryology, 11th Ed 2020 p 451, Fig 20.18, p 434 Fig 20.1]. For practical reasons based on trimesters, and to include the genital system, it is often extended to the first 13 weeks from the last menstrual period, but not to gestational week 16. Week 16 after fertilization marks the end of the sensitive period for serious cognitive disability (originally based on radiation exposure studies).	

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		Proposed change (if any): Resolve the confusion between gestational weeks and post-conception weeks and properly define the main embryonic period (weeks 3-8 after fertilization) and foetal period. In most TIS studies, the definition of organogenesis is from 4+0 till week 12+6 after the last menstrual period.	
165-166		Comment: The adverse pregnancy outcomes may only become apparent long after exposure has occurred, as the child develops, but they very much depend on when the exposure occurred. Proposed change (if any):	
169		Comment: The baseline risk of ~3% refers to major birth defects. Proposed change (if any): Add 'major' before birth defects.	
180-192		Comment: The whole paragraph is oversimplification of drug transfer into mother's milk. Drug transfer into milk depends on many factors: absorption, molecular weight, pKa, protein binding, elimination half-life, Tmax, timing of breastfeeding, presence of active metabolites, presence of transport systems. Infant (first two years of life) rather than child. Proposed change (if any): Rewrite and explain the complexity. Change to infant.	
197		Comment: Implantation is day 5 after conception, the first 2 weeks include additional crucial events such as gastrulation. Proposed change (if any):	
202-204		Comment: The term foetus refers to the narrow definition mention and not to the whole prenatal period. Proposed change (if any):	

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 co*
217-218		Comment: The definition of live birth depends on the duration of the pregnancy, as well as on birth weight and on signs of life rather than evidence of life. Proposed change (if any):	
234-236		Comment: Restriction rather that retardation is the updated term constituting IUGR. It is an ObGyn's term, which has to do with intrauterine life (low percentile according gestational age, decrease in growth percentiles over time) and it is not restricted to live born; and it is different than SGA which is a paediatric term that deals with birth weight percentile at delivery. Proposed change (if any):	
239		Comment: Signs rather than symptoms in the neonatal period. Proposed change (if any):	
246		Comment: Anomalies also include deformations. Proposed change (if any):	
258		Comment: Teratogen is not restrictive to medicines or environmental factors, it also includes infections, maternal diseases such as diabetes or lupus, radiation, or physical factors. Proposed change (if any):	
262		Comment: Not likely to cause serious rather than any medical or cosmetic problems. Proposed change (if any):	

Comments from:

Name of organisation or individual
[redacted]ENTIS, Pharmakovigilanz- und Beratungszentrum Embyronaltoxikologie, Charité Universitaetsmedizin Berlin, Germany

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3. General comments

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

4. 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)*
Line 145		Comment: Please indicate how gestational week is calculated. I presume after LMP. Proposed change (if any): Gestational week after last menstrual period (LMP)	
Line 147		Comment: Organogenesis and the definition of the first trimester, respectively, is not correct here (see Embryology books, e.g. Keith L. Moore et al. "The Developing Human", 9th edition, 2013). If organogenesis remains as defined here, namely until GW 16 after LMP, this can result in an underestimation of the birth defect rate in studies with not continuous drug exposure. This definition also contradicts what is said a little further down the text (line 199). Proposed change (if any): Gestational week 4-12: In the 10 weeks following conception, organogenesis occurs and can therefore be interfered with – resulting in major birth defects. …	
Line 151 and 155		Comment: How is late pregnancy defined? Renal insufficiency (line 157) after RAS-inhibitor exposure can already occur at/after gestational week 20 (after LMP). This is a functional renal defect. It might be added following line 151 Proposed change (if any):	
Line 169		Comment: The rate of 3% refers to **major** birth defects in live-births,	

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)*
		stillbirths and TOPFA (termination of pregnancy for fetal anomalies). I would like to refer to https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence Proposed change (if any): "Overall, the background rate for major birth defects at birth including live births/fetal death/ still births from 20 weeks gestation and TOPFA is at 3%."	
Line 213		Comment: According to national laws, stillbirth is defined differently.	
Line 214		Comment: please consider to add "missed abortion" Proposed change (if any): ***Miscarriage***: Spontaneous abortion, missed abortion and molar pregnancy.	
Line 236		Comment: Please add "and sex" Proposed change (if any): "… on the basis of gestational age and sex."	
Line 237		Comment: Please delete "malformations". Usually foetoxic effects do not include malformations. Proposed change (if any): "***Foetotoxic effect***: Alteration of foetal growth, functional defects caused by a medicine or other substance and which may be transient or permanent."	
Line 245		Comment: This is a very difficult subject. Definitions do not seem to be precise enough. Furthermore, some important terms are missing, for example, dysplasia, disruption, and deformity. Further, please define 'common variant' in order to differentiate it from minor birth defects. (Reference, e.g. Merks JHM et	

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		al, 2003; American Journal of Medical Genetics)	
Line 274		Comment: EUROCAT definition of total prevalence rate is =Number of cases among live births + fetal death from 20 weeks' gestation + TOPFA : Number of births (still and live births) (https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Full-Guide-1.4-version-15-Nov-2019.pdf) (page 131) It seems as if the presented definition here includes terminations for personal reasons in the denominator. This leads to a lower prevalence rate if the percentage of terminated pregnancies for personal reasons is high.	

Please add more rows if needed

Comments from:

Name of organisation or individual
[redacted] ENTIS [redacted] Charité – Universitätsmedizin Berlin, Institut für Klinische Pharmakologie und Toxikologie, Pharmakovigilanz- und Beratungszentrum Embryonaltoxikologie, Germany

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5. General comments

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

6. 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)*
Line 82		Comment: I think minor birth defects (e.g. simian crease) are not automatically a serious adverse reaction Proposed change (if any): In spontaneous reporting, the term 'adverse event' is synonym to (suspected) adverse reaction and all major/relevant birth defects are (suspected) 'serious adverse reactions' (see GVP Annex I).	
Lines 14-143		Comment: Also effects on pregnancy might be possible like premature labour, gestational diabetes, pre-eklampsia Are prematurity and intrauterine growth retardation included in fetotoxic effects/events on the neonate? Isn`t it more a implantation siturbance? Proposed change (if any):	
Lines 145-146		Comment: Is this really an early pregnancy loss? Many sources define an early pregnancy loss during a loss during first trimester Proposed change (if any):	
Lines 147-150		Comment: Period is too long, I would suggest to use the definition of first trimester Proposed change (if any):	

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)*
Lines 151-154		Comment: It is true that major malformations develop during first trimester and this might be the more dangerous exposure time; still there are several risks later (cns damage, fetotoxicity e.g. due to sartans or ACE inhibitors). The statement in this lines sound very harmless to me. Proposed change (if any):	
Lines 160-162		Comment: It is true, that pregnancy losses lead to an underestimating of birth defects, but stillborn children normally get an examination in which birth defects can be detected Proposed change (if any):	
Line 210-213		Comment: The definition of stillbirth varies from country to country. In Germany: no evidence of life and at least 500g independent from the gestational week Proposed change (if any):	

Please add more rows if needed.

Comments from:

Name of organisation or individual
[redacted] University of Manchester and Royal Manchester Children's Hospital* *There may be some overlap between the following comments and those in the response generated on behalf of ConcePTION WP6. [redacted]

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7. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The experience with isotretinoin and sodium valproate demonstrated that the impact of a medicinal exposure on the developing brain can be detrimental and effect a greater number of children that structural malformations. Whilst longer-term outcomes such as brain functioning are mentioned with some frequency in this document, structural teratogenicity is still given central consideration and prominence. Specific comments below are provided to highlight opportunities where wording could be altered or added to provide more guidance around non-malformation endpoints. Of importance, it is unclear as to when and under what conditions a PASS study would be requested to investigate longer term chid outcomes and if required, which outcomes within the neurodevelopmental category should be researched and who would conduct such studies.	

8. 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)*
82-85		Comment: This focuses on structural malformations mainly. Proposed change (if any): Additional wording could be added to include functional teratogenicity outcomes such as neurodevelopment.	
145-163		Comment: The wording currently could be understood to suggest that the impact of an exposure on the brain only occurs after organogenesis. Proposed change (if any): Suggest rewording to highlight the susceptibility of the brain throughout gestation and beyond into childhood; which has relevance for breastfeeding exposure.	
180		Comment: This section identifies that there may be immediate effects on the neonate from breastfeeding but does not consider that exposure to medications through breast milk conveys a prolonged period of exposure which may pose a risk to on going brain development.	

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)*
		Proposed change (if any): Suggest re wording to reflect the possibility of a potential impact on brain development from exposure to medicinal products through breastfeeding.	
206-275		Comment: Whilst terminology with regards to birth defects is outlines there is no such glossary for neurodevelopmental outcomes. The consideration of neurodevelopmental outcomes has recently become more central in pregnancy pharmacovigilance and there is often a large misunderstanding about what this term refers to and the different aspects of brain functioning which fall under this umbrella term. Proposed change (if any): Suggest adding in a similar style of glossary for the most important neurodevelopmental outcomes.	
355-356 & 510-515		Comment: The current wording here describes studies or spontaneous reports as 'prospective' only if recruited prior to ultrasound. This is very much biased towards structural malformations. For important functional outcomes such as neurodevelopment or child health, recruitment at any time up to the end of pregnancy would be considered 'prospective' as the outcome of interest is not yet known.	

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)*
		Proposed change (if any): Suggest additional wording noting that prospective enrolment may be classed differently for different child and maternal outcomes.	
379		Comments: Table P does not include any examples of where functional or longer-term outcomes are being reported. Proposed change (if any): Suggest additional example and reformatting of the table to include a wider variety of outcome examples.	
418-419		Comment: There is an opportunity here to highlight that the investigation of teratogenic outcomes should now be wider than that of major structural malformations. Proposed change (if any): Suggest additional wording highlighting the central importance of other outcomes (including neurodevelopment and child health).	
477-480		Comment: It is not clear here as to what the threshold for use of a product in pregnant women is in order to then require further PASS studies looking at maternal and child outcomes/risk. Proposed change (if any): Suggest that a tangible threshold is outlined in terms of frequency of use in pregnant women which would lead to the requirement of	

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)*
		further PASS studies looking at teratogenic outcomes (structural and functional). Further it would be useful clarification as to who would be undertaking the additional PASS studies into teratogenic risk, should they be required.	
482		Comment: Similar to the comment above, it should be made clearer as to who and how it is decided that additional PASS studies, beyond simply drug utilisation, are required. Further some discussion about who is best placed to undertake these studies would be useful. Proposed change (if any): Suggest additional wording to provide clarity.	
490		Comment: It is currently stated that due to the rarity of outcomes, studies 'across different countries are likely'. This is certainly the case for rare outcomes such as specific types of structural defects, however in more commonly observed outcomes, which are investigated with sensitive measures, smaller cohorts from a single country can provide adequately powered cohorts. Proposed change (if any): The current wording surrounds rare outcomes such as specific birth defects but should be modified to reflect that different outcomes are likely to	

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)*
		require different approaches both in terms of methodology and cohort sample size.	
527- 541		Comment: This sections reads as though longer term outcome studies will be an optional extra to PASS studies looking at teratogenic risk and suggests that structural malformations will remain as the central feature in risk identification. This goes against what we know about how teratogens impact on the development of the fetus and the varied yet important outcomes which can be produced. The substantial life time impact of certain child health and neurodevelopmental functioning highlights the significance of ensuring that non-structural endpoints are also considered. Proposed change (if any): Suggest additional wording regarding the importance of these outcomes and in what situations longer term outcome studies must be completed (i.e. when there is an identified structural malformation risk, when another drug in that class is implicated as altering fetal brain development).	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 FEB 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
EUCROF Pharmacovigilance Working Group

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
None	EUCROF Pharmacovigilance Working Group is pleased to have the opportunity to provide their comments on this document and potentially contribute to its improvement.	n/a

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)*
Line 44-47		Comment: There seem to be not sufficiently robust opening statement justifying the need of this document. Proposed change (if any): Instead of the text in lines 44-47 insert the following: "The need for guidance on conduct of pharmacovigilance during pregnancy and breastfeeding is absolutely unequivocal as these population groups (also referred to as special or vulnerable) are often excluded from the exposure to medicinal products during their clinical development. Consequently, for many marketed medicinal products, their characterisation in these vulnerable population groups remains limited or even unknown and as such included in the domain of missing information of the corresponding RMP. Moreover, effects of exposure to medicinal products during pregnancy and breastfeeding can be influenced by physiological changes to many functions of pregnant women body and can have potential effects on the unborn child or breastfed infant".	
Line 45		Reference source to the statement "widely recognized" would be appreciated.	
Line 379 (Table P III.1)		Comment: 2nd situation (No adverse reaction in child): In this situation, the table describes 'No case[7]'. This could misguide readers, at this could be interpreted as no case is	

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)*
		required. It, however, means, no case should be reported. GVP VI describes: When no reaction is reported for the exposed child/foetus, the parent-child/foetus report does not apply. Only a parent report should be created to describe the child exposure to the medicinal product. The patient characteristics refer only to the parent (mother or father) who may as well experience adverse reactions with the suspected medicinal product. Reports with no reaction should not be submitted as ICSRs (see VI.B.6.1. for general guidance on the management of these reports). Proposed change (if any): Add a table note explaining 'A parent report should be created to describe the child exposure to the medicinal product. The patient characteristics refer only to the parent (mother or father). Reports with no reaction should not be submitted as ICSRs.'	
Line 760		Comment: typo: instead of "period" it should be "periodic" Proposed change (if any): change to "periodic"	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual

[redacted]

On behalf of EULAR

1. General comments

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

This is a very complete and well detailed document that can be very useful for conducting clinical trials and, more in general, clinical studies in pregnant and breastfeeding patients.
I have listed below some suggestions for the text:
Page 3, introduction: I suggest mentioning that the need on pharmacovigilance for drugs used during pregnancy and lactation is specifically increased by the actual better management of chronic disorders, that allow a better quality of life of chronic patients including also family planning (I think that is important to mention the concept of chronic disease, that are now the large majority and will increase in the future).
Page 5, P.III.A.1.3. In the list of "possible negative consequence of exposure" I think could be included preeclampsia (hypertensive disorder of pregnancy) causing preterm delivery (with all the consequence of prematurity). In fact, preeclampsia has been associated (as an example) to the administration of drugs (corticosteroids).
Page 7, on line 225 is indicated "pre-term birth" as delivery before 37 weeks of gestation. It could be worthwhile to indicate also "very pre-term birth", that is a delivery before 34 weeks of gestation. This second definition include very premature babies with a different and eventually more severe prognosis than those born between 34 and 37 weeks.
Page 7, line 234: "growth retardation" in the recent literature is mentioned as growth *restriction* (to avoid misunderstanding).
Page 7, on line 243: "withdrawal syndrome" can occur also in children born to mothers chronically using corticosteroids.
Page 9, on line 301: the concept is very important and could be underlined suggesting to use as much as possible a control group of patients, suffering the same disease, but not exposed to the drug under study
Page 14, on line 473: among the "potential confounders" the presence of concomitant medication in the patient treatment should be taken into account.

Page 15, on line 511: retrospective cases can be very useful, but only if collected as cohort of a defined disease (like in registries) ; to introduce one single case or to let patients introduce their own case, can cause bias.
Page 23, on line 818-822: systemic autoimmune rheumatic diseases should be included among medical disorders that ca be considered risk factors for adverse pregnancy outcome.

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)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from: Compiled comments from consortium

Name of organisation or individual
EUROmediCAT (www.euromedicat.eu)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	These GVP guidelines are important and welcome. EUROmediCAT members have submitted specific line-by-line comments through other respondent groups (ISPE, CONCEPTION) and here we will only summarise some of the main points.	
	A **benefit-risk framework** could be further emphasised throughout the document, for both pregnancy and breastfeeding exposures.	
	"**birth defects in general should not be studied as one single outcome**" (line 179) – we agree this is very important as teratogens usually have specific effects. While sample size may make this difficult in the early stages post-marketing, safety studies should continue until risk of specific birth defects can be properly assessed.	
	Terminology: There are too many terms for congenital anomaly on page 8 and we propose our EUROCAT definitions, used by 49 registries in 23 countries. They can be found in Guide 1.4 and in the syndrome guide.https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-	

	collection/guidelines-for-data-registration#inline-nav-2	
	Total Prevalence rate definition (line 274). Please also use well accepted EUROCAT definition. Proposed change: *Total prevalence rate is* *number of cases among live births, stillbirths and* *terminations of pregnancy for fetal anomaly* *Number of live births and Still births* Note: numerator refers to terminations of pregnancy for fetal anomaly (i.e. after prenatal diagnosis). The acronym is TOPFA Denominator should not include terminations.	
	Confounding by indication (lines 300-307) "the background rates of adverse pregnancy outcomes in the target populations may need to be specified in the RMP". This section needs to recognise more clearly that rates of an outcome in a population (with and without the disease in question) depend on study methodology and data source, and that an unmedicated population may not be available or comparable (e.g. unmedicated epilepsy is not comparable to medicated epilepsy). Therefore, a range of methods for assessing confounding by indication may be required.	

	Lactation: Inclusion of lactation guidelines is welcome, but more detail could be added including initiation and colostrum, and stage of breastfeeding. Exposure of infant during lactation may lead to immediate or late adverse outcomes. When examining late outcomes of pregnancy exposure, it may be relevant to consider both effect of medication on breastfeeding (initiation, duration) and effect on infant of exposure during breastfeeding.	
	Safety Communication: The guidelines could mention consideration of healthcare to be recommended in case of teratogenic medication exposure, including third trimester ultrasound, and early neonatal and childhood screening.	
	Risk minimisation: Risk minimisation should include intensified efforts to ensure appropriate prescribing in women of childbearing age to avoid unnecessary exposure.	

	.	

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)*

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
European Organisation for Rare Diseases
[redacted]
And also [redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EMA approach EURORDIS welcomes the new regulatory approach which consists in providing women and healthcare professionals with the information needed for them to decide together which treatment is best indicated when a pregnancy is planned, or which action to decide if a pregnancy is discovered while the woman was on treatment. With this, we are moving away from SmPC / package leaflet instructions for use that were not really helpful to make decisions ("not recommended", "use with caution", "preferable to avoid", "should not be used", "contra-indicated"). For example, some products are known to expose to risks only during the first 2 months of pregnancy, and a complete ban over the entire 9 months is not scientifically justified. Need to include these aspects in all discussions on precision medicine When a potential risk exists, rather than to systematically contra-indicate the product during pregnancy, to provide more personalised medical advice. Healthcare professionals who are part of the European Network of Teratology Information Services (ENTIS) are best placed to give advice on pregnancy and/or breastfeeding. **Vaccines**	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The guidelines do not specify information needed for vaccine development, or how to communicate on risks with vaccines during pregnancy / breastfeeding. Maybe to add a dedicated chapter. **Advanced therapies** Same question for advanced therapies, whether some specific recommendations are needed, or maybe to remind main pharmacovigilance measures. This is important for long-term effects of the advanced therapies in new-born across generations. **Assisted Reproduction Techniques (ART)** Maybe a chapter on ART would be welcome. This is a special population within a special population, but as these techniques are more often used, a larger number of women are now exposed. France recently adopted a legislation whereby any woman could access ART, even if not medically justified. Despite the ambiguity of the studies, reviews of studies conclude that children born following ART are at increased risk of birth defects compared with spontaneous conceptions (Kurinczuk et al., 2004; Hansen et al., 2005). In any case, the use of ART to initiate the pregnancy should be documented, as ART expose both the woman and the foetus(es) to adverse reactions: For women: hypertensive disorders, pre-eclampsia, thrombo-embolism, urinary tract infection, anaemia, vaginal-uterine haemorrhage (placental abruption, placenta previa), and fluid overload in association with parental tocolysis, ectopic pregnancy.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Hansen et al. (2002) concluded that infants conceived with use of intracytoplasmic sperm injection or in vitro fertilisation have a twice as high risk of a major birth defect as naturally conceived infants. **Other special populations** Even if in most cases these other conditions prevent the person from becoming pregnant, some conditions exist which require special attention: 46 XX (female pseudohermaphroditism), triple X syndrome, fragile X syndrome… Anti-epileptic products are usually prescribed, or antidepressant, psychostimulant, neuroleptic, anxiolytic… During pregnancy, suppression of the overproduction of androgens by the foetal adrenal gland is achieved by giving the mother a daily dose of 20 µg of dexamethasone per kilogram of maternal weight, split in two or three doses. Of course, such treatments are propose din highly specialised centres where the woman receive all necessary information, and they are rare. Rare but not to be ignored.	

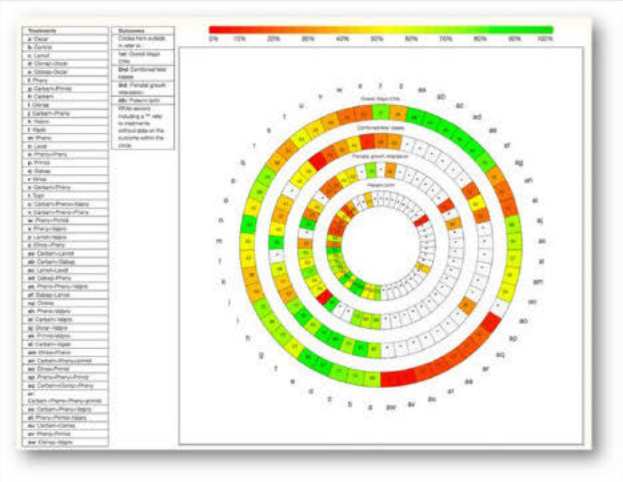
2. Specific comments on text

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)*
Lines 62-64		Comment: EURORDIS acknowledges the difficulty to obtain pre-authorisation data due to restrictions of clinical trials in terms of size, time and duration of follow-up and to the inclusion and exclusion criteria for selecting participants, women and pregnant women in particular. However, Cochrane reviews seem to indicate more trials enrol pregnant women than usually though (after first 2 months of pregnancy, usually around month 5 or 6). PKPD during pregnancy is frequently assessed. EURORDIS would welcome some thorough analysis of the availability of such data in EMA scientific Discussions / SmPC. When gaps exist, some reflection should be initiated to understand the reason why (scientifically justified or not. Not could include absence of experience in the company / CRO with recruitment of pregnant woman in clinical trials, reluctance of some IRBs to authorise their recruitment…).	
Lines 106-124		Comment: P.III.A.1.1. Availability and interpretation of data Animal studies: animal pregnancy duration can be an obstacle. New techniques permit in vitro toxicity testing shortly after pregnancy has started (at day 9 after fecundation). These tests are not perfect and they could complete pre-clinical testing. If a drug test is negative on at least one animal species, the risk for humans is very low.	

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)*
		This maybe falls in the scope of IMI Topic 9: ConcePTION – Continuum of evidence from pregnancy exposures, reproductive toxicology and breastfeeding to improve outcomes Proposed change (if any): To add the possibility to complete pre-clinical studies with in vitro toxicity testing, or to recommend more research to develop an in vitro assay.	
Lines 106-124		Comment: In some animal studies, the only abnormality is one extra rib. There are no consequences to live with an extra rib. So why to contra-indicate the use in pregnancy when extra rib detected? Some drugs do not have a warning sign (black triangle) even with positive animal tests: the reason is that animal tests are considered to have not sufficient clinical relevance for human beings.	

Lines 461-473		Comment: Among epidemiological studies, EURORDIS expected to read some guidelines following PROTECT IMI research in pregnancy, with direct-to-patient pharmacovigilance research. Acknowledging difficulties to register women and such programmes and to collect all necessary information, including pregnancy outcomes, EURORDIS opinion is that more participation of women in data collection is welcome.	
Lines 492-526		Comment: Pregnancy registries In line with comment above, for women to report directly during pregnancy and/or breastfeeding, a mobile app such as Web-RADR mobile application could be useful. Same for midwives.	
Lines 616-665		Comment: Problem when patient taking several drugs and seeing several doctors, each doctor push one type of information on the medicine he/she prescribed. There is a sometimes discordance of viewpoints (some say "no treatment", other say "no pregnancy"), but women want to get pregnant anyway. How are these pregnancies managed then?	
Lines 640 - 665		Comment: Information on risks if disease left untreated is missing There are two different levels of daily practise for specialist. Need to compile a lot of information in order to make an informed choice. Difficult to provide the specific information adapted to each situation. Investigate women's real desire to become pregnant. - Expose the risks - Inform that pre-natal screening is available, when the case - Impact of drug on embryo - Effect on women if treatment interrupted	

		- Women exposed to pharmaco-active risk: the duration of exposure might enter into consideration	
Lines 640-643		Comment: Pregnant women cannot rely on product information when they need a treatment: printed product information is given after prescription. Electronic product information might help compare different products in the future. For the women to make an informed decision, and weigh the risks of different medicines, reading different package leaflets will not be the solution. They won't get them all, only the ones of the prescribed products. Of course, healthcare professionals should know, but maybe the women would like to get some information before they see their doctor. Women taking medicines and planning to become pregnant would also need comparative information on different products to treat their disease and the risks on their future foetus. Package leaflet provides information for one product only. Education materials should exist for each disease, with graphic visualisation tools. Example below: *Counselling / pregnancy and epilepsies* *49 treatments / combinations* *96 eligible studies (58,461 patients)* *Rank heat plot for overall major congenital malformations (CMs), combined fetal losses, prenatal growth retardation, and preterm birth. Rank-heat plot of 49 treatments (presented in 49 radii) and four outcomes (presented in four concentric circles). Each sector is coloured according to the SUCRA value of the corresponding treatment and outcome using the transformation of three colors: red (0%), yellow (50%), and green (100%).*	

		 *Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Medicine. 2017;15:95. doi:10.1186/s12916-017-0845-1* Working group with toxicologists, clinicians, women, and other specialists (embryologists, pharmacologists, paediatricians, obstetricians, communication specialists) should be set	
Lines 666-694		Comment: In case of exposure, the leaflet should advise whom to contact to get further advice (ENTIS experts etc.). ENTIS (https://www.entis-org.eu/), the global collaborative network of Teratology Information Services, with 30 agencies across Europe and beyond, aims to coordinate and collaborate the activities of the different Teratology Information Services (TIS), and to collect and	

		evaluate standardised data in order to contribute to the primary prevention of birth defects and developmental disorders	
Lines 719-721		Comment: Special efforts needed to inform and create the dialogue with women who might have conditions that affect their ability to understand risks or make adequate decisions. Proposed change: Patient alert/reminder cards should provide succinct messages on the potential for harm, the need for contraception, action to take in the event of an unplanned pregnancy and action to take if planning a pregnancy, as applicable. Different educational materials may be appropriate for different women (teenagers, pre-menopausal women, women with cognitive difficulties).	
Lines 761-764		Comment: Marketing authorisation holders have an obligation to report pregnancies exposed to their products in the PSUR, but there is no obligation on doctors to report pregnancy outcomes to MAH or to anyone. MAH often have difficulties accessing pregnancy outcomes information, unless they pay to obtain them.	
Lines 817-822		Comment: **Medicines versus other chemicals** Endocrine disruptor in particular, but many other chemicals, can induce effects in pregnant woman, in foetus, or during breastfeeding. This is mentioned in maternal medical history, and maybe joint work with the European food Safety Authority would be useful.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Food and Drug Administration (FDA)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	We appreciate the opportunity to provide comments. The document lists examples of different types of pharmacovigilance related to pregnancy and lactation outcomes Consider providing an explicit opening statement indicating that the focus of this document is fetal/child related AEs.	

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)*
46		Comment: We acknowledge that there may be regulatory differences between the US and the EU and would like to share that the US federal regulations related to clinical research no longer refer to pregnant or breastfeeding women as vulnerable, as stakeholders feel that this terminology is derogatory and that pregnant or breastfeeding women have the capacity to make their own decisions. Therefore, we have abandoned reference to pregnant or breastfeeding women as vulnerable.	
120 121-122		Comment: The sentence "breastfeeding women are usually excluded from clinical trials" may be too strong; please consider revising to: "breastfeeding women have historically been excluded from clinical trials". Comment: Estimation of risks for breastfed infants are affected by a multitude of factors. Proposed change (if any): When providing examples, ensure verbiage reflects one of multitude examples. For lines 121-122, consider changing verbiage to "factors that help estimation of risks for breastfed infants may include but are not limited to pharmacokinetic (PK) data"	
533		Comment: Consider providing examples of other long-term outcomes. In addition to neurodevelopmental outcomes,	

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)*
		consider other outcomes such as growth and sexual development Proposed change (if any):	
579		Comment: Consider including a calculation of the estimated daily infant dose. We have had recent feedback that prescribers are misinterpreting the relative infant dose and applying the information incorrectly when assessing infant drug exposure via breast milk.	
739		Based on the 2012 FDA Drug Safety and Risk Management Advisory Committee Meeting, the theoretical risk and the limited available evidence regarding transfer of a drug of teratogenic potential through seminal fluid to a pregnant woman suggest a low plausibility of potential risk, even if the drug were present in the semen. This concept was not fully adopted in the FDA Guidance on Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations.	
809		Comment: For maternal weight and height, please specify pre-pregnancy or post-pregnancy weight Proposed change (if any):	

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)*
837		Comment: Consider addition of e-cigarettes to the list of substance exposures Proposed change (if any):	
848-849		Comment: Consider adding prompt for maternal family history of developmental delay, genetic conditions Proposed change (if any):	
851		Comment: Recommend adding prompts for paternal family medical history Proposed change (if any):	
873		Comment: Consider guidance on timeframe for follow-up for neonatal information for data consistency Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Ferring Pharmaceuticals A/S, Copenhagen, Denmark

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Ferring acknowledges the importance of updated guidelines for the vulnerable special population of pregnant and breastfeeding women. Ferring is pleased to note that this draft pregnancy and breastfeeding Guideline, as opposed to the current Guideline from 2006, no longer excludes 'medicinal products authorised for pregnancy-related symptoms and disorders or pro-fertility drugs', thereby giving more clear guidance regarding case handling of these products than GVP Module VI. For increased clarity, we suggest mentioning this product inclusion specifically in the Guidance. In addition, Ferring proposes to further clarify expectations for follow-up of pregnancy outcome in medicinal products indicated for use in obstetrics or pregnancy, and to exclude the requirement to add a 'Drug exposure in utero' event for these product. Please see detailed suggestions 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')*	Outcome *(To be completed by the Agency)*
98-100		**Comment**: Request for scope clarification, regarding inclusion of products with labelled indication in assisted reproduction, obstetrics and pregnancy. **Proposed change (if any):** Medicinal products with labelled indication in assisted reproduction, obstetrics and pregnancy are included in the scope of GVP P.III. The effects of medicines on fertility and the use of medicines in neonates are out of scope of GVP P.III; guidance on these areas is provided in GVP Module V on risk management planning and GVP Chapter P.IV on the paediatric population.	
314-319		Comment: An explanatory sentence is proposed. As currently stated, every patient exposure is implicitly expected to be captured for products with obstetric or pregnancy indications. **Proposed change (if any):** Spontaneous reporting during the post-authorisation phase is one primary source of information on adverse reactions occurring following exposure in utero or during breastfeeding. Reports where the embryo or foetus may	

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)*
		have been exposed to (a) medicinal product(s) (either through maternal exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth. For products with labelled assisted reproduction, obstetric or pregnancy indications, cases only require collection of information about the pregnancy outcome if an adverse reaction is reported in the mother or the foetus/neonate.	
320-322		Comment: Please specify 'authorised for use' in the below sentence; does it refer to products with indication in pregnancy, or to products with no pregnancy or breastfeeding related contraindications, warnings or precautions, or both? Relevant distinction for products with obstetric or pregnancy indications. **Proposed change (if any):** It is essential that marketing authorisation holders and competent authorities in Member States collect and provide as many elements as possible for all cases, irrespective of whether or not a product is authorised for use in pregnancy or breastfeeding, to facilitate the evaluation.	
333-338		**Comment**: For obstetric products and products indicated in pregnancy, it is implicit that all cases are related to drug	

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)*
		exposure in utero. Inclusion of an event with MedDRA term 'Drug exposure in utero' therefore does not add scientific value for these products. adds to the administrative case burden for these types of drugs. For data analysis purposes, separation of mother and foetus cases is identified via other data fields, such as Route of administration (transplacental) or Patient Age group. **Proposed change (if any):** – for the route of administration, code, in the case of exposure in pregnancy leading to pregnancy loss or other adverse pregnancy outcomes, the route of administration as 'transplacental' and use the MedDRA term 'exposure in utero' in the Reaction/event section (MedDRA term not applicable for obstetric medicinal products or products with a labelled indication in pregnancy); and in the case of exposure during breastfeeding, code the route of administration as 'transmammary' and use the MedDRA term 'Drug exposure via breast milk' in the Reaction/event section. The route of administration for the mother should be coded in the data elements, parent section of the parent-child report;	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10-Feb-2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Gilead Sciences

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1. General comments

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

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)*
Lines 333 -335		Comment: "-for the route of administration, code, in the case of exposure in pregnancy leading to pregnancy loss or other adverse pregnancy outcomes, the route of administration as 'transplacental' and use the MedDRA term 'exposure in utero'..." Per Table P III. 1 in this draft guidance, pregnancy loss only requires creating only 1 mother case. With no baby case being created for this scenario of pregnancy loss, this coding guidance does not seem applicable. Proposed change (if any): Please consider removing reference to "pregnancy loss" or clarify that coding guidance is in reference to baby case only.	
Line 379-380 or Table P III.1		Comment: "2nd situation: No adverse reaction in mother and ..." This implies that no Mother case is created to capture pregnancy exposure if there is no event for mother or baby. Please confirm if there is still expectation for MAH to capture/evaluate all pregnancy exposure cases (i.e. report of exposure to company product during pregnancy).	

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)*
		If no mother case is created (for those reports with no event in mother or baby), please advise on how MAH should monitor/account for all pregnancy exposures. Proposed change (if any): Please consider providing more guidance on Twins scenarios (e.g. ADR in mother but not in twins, ADR in one of twins, etc.)	
Lines 767-769		Comment: Recently our company was requested to compare our birth defect data with EUROCAT prevalence rates. This requires Company to code data using ICD-10, in addition to commonly used MedDRA coding. Will this be the expectation of EMA moving forward? If not, are there other relevant prevalence rates using MedDRA available for companies to compare data to?	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
ICON Clinical Research

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1. General comments

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

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)*
Line 300 to 307		Comment: The current RMP template already includes instruction in SIV.3 to include discussion on rates of pregnancy outcomes for the non-target population Please further clarified to specify rates of 'adverse pregnancy outcomes in women with specific conditions' as applicable to the indication. Proposed change (if any):	
Line 308 to 312		Comment: Section V2 of the RMP provides allowance for additional RRM to include pregnancy protection programmes, as defined in the EU RMP guidance; however, additional text can be added to the template to clearly define relevant examples for clarity. Proposed change (if any):	
Line 390 to 403		Comment: We understand this to be interval as opposed to cumulative but this doesn't seem to be explicitly stated. Can this be clarified? Proposed change (if any):	

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)*
Line 443- to 444		Comment: Will there be any minimal period and format for a follow-up to monitor achieving developmental milestones suggested by the Agency? Proposed change (if any):	
Line 753		Comment: At what point would we find out whether there is a PPP? Should this be a checklist item? Can we get clarity on where in the PSUR this data should be presented e.g. in effectiveness of risk minimisation measures appendix? Proposed change (if any):	
Line 763		Comment: We understand this includes missing information as opposed to only risks, as missing information is part of the summary of safety concerns. can we get clarity on this point? Currently, updates to missing information is only required for the reporting period - would this change now to require cumulative information now? Can we get clarity on this? Proposed change (if any):	
Line 763		Comment:	

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)*
		1. Would separate tables for interval and cumulative data be needed? Can we get clarity on this? 2. Does the table needs to be completed in all instances? If there are very few cases, would a narrative format be appropriate for interval data? Can we get clarity on this? 3. It's not entirely clear what is required for products without specific pregnancy concerns. We understand we still need to provide the same level of data but the table itself isn't required? What about interval vs. cumulative? Can we get clarity on this? Proposed change (if any):	
Line 770		Comment: The footnote states: "The observed phenotype should be specified". How? Easy if not many cases but if there are a lot of data then we would like some guidance on how the data should be presented (i.e. how much specificity). Can we get clarity on this? Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 Feb 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Innovative Medicines Initiative ConcePTION Consortium

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The experience with isotretinoin and sodium valproate demonstrated that the impact of a medicinal exposure on the developing brain can be detrimental and affect a greater number of children than structural malformations. Whilst longer-term outcomes such as brain functioning are mentioned with some frequency in this document, structural teratogenicity is still given central consideration and prominence. Specific comments below are provided to highlight opportunities where wording could be altered or added to provide more guidance around non-malformation endpoints.	
	Of importance, it is unclear as to when and under what conditions a PASS study would be requested to investigate longer term chid outcomes and if required, which outcomes within the neurodevelopmental category should be researched and who would conduct such studies.	
	This document is important and much needed. Some revisions, as below, would complete and strengthen the document.	
	The potential for medicines to affect breast milk production is mentioned in several places, without	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	including the potential to disrupt the complex physiology of the initiation of lactogenesis e.g. p.3, p.6 moves from anomalies to exposure via breastmilk. Colostrum is not mentioned.	
	The stage of lactation should be mentioned e.g. if lactation is established or the infant is >6/12 and partially weaned, medicines may have different impacts.	
	Table P.III.2 should have rows for: pre-term birth <32 and <37 weeks, SGA <3rd and <10th centiles, breastfeeding rates at specified times, developmental delay, school performance, fertility.	
	'Birth' is generally preferred to 'delivery'. A delivery refers to a single event. In the case of twins, it is two births and one delivery.	
	Very interesting and useful document	
	Is an update "from data to labelling" planned?	
	There are too many terms for congenital anomaly on page 8 and propose that EUROCAT definitions are used.	
	The 49 congenital anomalies registries in 23 countries that make up EUROCAT and underpin pharmacovigilance studies should have their current definitions accepted and this would maintain consistency in the published literature.	
	Perhaps more description regarding parameters for control groups	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Although this GVP guideline deals with pregnant and breastfeeding women, some remarks about paternal exposure are welcome. This is partially addressed in line 117 but may be elaborated. Combining the text on paternal exposures in a separate paragraph might be useful	
	Put more emphasis in the document on: Importance of knowing the exact timing of exposure in studies, as uncertainties due to estimates or assumptions on intake and the timing might dilute the power	
	Background incidence of outcomes should be ideally addressed within the study itself, as these might fluctuate dependent on the study method	
	Accuracy of essential covariables / confounding factors is dependent on method of data collection	
	Ideally be able to distinguish missing data from information that can be assured is not applicable (in e.g. Heading P.III.A.1.3, lines 487 -491, Heading P.III.B.4.2.3)	
	In the GVP there is a focus on activities of a specific medical product. However, as pregnant or breastfeeding women it is also of interest to be able to compare the potential teratogenic effects between medicinal products used to treat the same disease, so instead of a drug specific focus, I think it also should be encouraged to have a disease specific focus in for example PASS studies.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	In line 487 it is mentioned that epidemiological studies should preferably be carried out using existing data sources and preferably designed in such a way as to minimise bias and confounding. Although we agree with this, we also think it is important to mention that there is a lack of high-quality data in this field, and that there is also room for primary data collection to get the data needed.	
	In the section on pregnancy registries more emphasis may be needed to try to avoid medicinal product specific registries and use other options.	
	While the concept of PK (line 121) to estimate risks for breastfed infants at time of marketing authorisation, the developing field of physiology-based pharmacokinetics (PB-PK) is likely also a very valuable approach to further improve the current setting (initial estimation of potential risks) and this tool holds also the potential to guide PK study development. It somehow worth to notify that besides appearance in human milk, that also absorption characteristics of the newborn or infant after oral ingestion is a relevant factor to estimate risks. Also, this part can be estimated by such PBPK models.	
	From a clinical perspective, the document reads somewhat unbalanced, as not providing breastfeeding is a 'nocebo' as associated with negative effects on the newborn, infant, in paediatric life and beyond and	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	these effects are not limited to neurocognitive outcome. To illustrate this, the data collected within the MONEAD study clearly illustrate that lactation during maternal AED intake results in better neurocognitive outcome compared to formula feeding following AED exposure during pregnancy.	
	Only reporting on adverse events following lactation related exposure is a construct that results in a unbalanced dataset to assess, and should be weighted to 'control-formula' datasets in neonates and infants (neither exposed to maternal drugs, not to human milk), somewhat similar to the approach taken to assess 'teratogen' effects of drugs during pregnancy. Along the same comment (eg line 180), GPV chapter P.IV (paediatric population) is relevant to provide information and structure on how to assess and report on neonatal or infant related aspects on PV, but the PV IV chapter neither mentions the lactation setting.	
	Very useful Guidance. The emphasis on not grouping birth defects into one category is very welcome. Some further clarity needed as to the range of methods that may be needed to account for confounding by indication for treatment, as a suitable unexposed disease comparator may not be feasible. Risk minimisation should include efforts to ensure appropriate prescribing, avoiding unnecessary exposure. Some terminological confusion needs to be	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	attended to.	
	This document compiling terminology, definitions and coding requirements is welcomed and will be helpful to address the specificities of Pharmacovigilance in this population.	
	Immunization clinical studies in pregnant women are conducted with the purpose of immunizing the foetus, other vaccinations are indicated in this population like Flu or tetanus. Vaccines do not cross the placenta, so there is no a true exposure to the medicinal product. It would be useful to add guidance on the specific case of immunization during pregnancy or lactation (e.g. event term coding, route of administration, follow-up requirements).	
	In the whole document, more guidance is provided to manage information from pregnancy exposure than for exposure through lactation while the needs are the same. For example, there is no app 1 bis: questionnaire to collect information during exposure through lactation.	
	PSURS are key to summarize information on Benefit Risks ration during the period under review. Both section B3, PSUR, and section C1, operation of the EU network, give instructions on description of risks of medicines during pregnancy and lactation. A consolidation of instructions from these sections would help, especially for requirements in table III.2 for	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	specific presentation and analysis for data collected in pregnant women.	

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)*
1		Comment: Appendix 1 is a very valuable document, that structures pregnancy and pregnancy related outcomes. However, a similar structured approach to collect information on lactation related exposure or events (maternal e.g. milk volume, or newborn/infant) is not yet present in this guideline version. Proposed change (if any): to be added, or indicate the need to develop such a questionnaire	
5		Comment: What is the reference for such a division of gestational weeks. It does not really match with the terminology after; In the paragraph "late pregnancy and during delivery ", the potential effects of drugs used at delivery could be added. Proposed change (if any): see above	
6		Comment: for some embryologists, the organ-forming-period (with a high sensitivity to teratogens) begins at day 13 post conception.	
61		Comment: Breast milk INITIATION AND production	
67		Comment: Not sure in practice that information available on pregnant / lactating women is more available to the MAH, considering that access to these data is limited to spontaneous reports, or to data collection schemes established nationally or by the MAH. Statement should be	

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		qualified. Proposed change (if any): Whereas historically, obtaining data from pregnant women on medicine use and outcomes during the post- authorisation phase has been challenging, it is becoming increasingly feasible via national registries or organized data collection schemes established by MAHs to access data and generate knowledge on safety in this population. Spontaneous reporting rates for this information remain low.	
69		Comment: it is becoming increasingly feasible to access data and generate knowledge on safety in this population. Proposed change (if any):Please address the quality and completeness of these data	
71		Comment: Replace 'enable' with 'ensure'.	
73		Comment: "well-informed about uncertainties" – agree this is very important. However, communication of uncertainties does not appear in lines 616-665. Proposed change: Include communication of uncertainties in PIIIB6.	
82		Comment: This focuses on structural malformations mainly. Proposed change (if any): Additional wording could be added to include functional teratogenicity outcomes such as neurodevelopment.	
98		Comment: In line with the general comment made, the relevance of the guideline on the use of medicines in neonates should probably not be considered out of scope of GVP P.III, or at least alignment between these guidelines	

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		should be pursued. Proposed change (if any): suggest changing out of scope statement.	
102		Proposed change (if any): delete 'usually' or define circumstances where this does not apply.	
110		Comment: Please give examples, and references.	
139		Comment: This should specify elimination half lives in women, foetus, term and preterm neonates.	
140		Comment: Clinically, gestational age is usually calculated from the last menstrual period, but more accurately 140 established from ultrasound diagnostics. Proposed change (if any): true indeed, but out of the scope of this paragraph	
141		Comment: Possible negative consequences of exposure include early pregnancy loss, births defects (teratogenicity), foetotoxic effects, adverse events on the neonate and delayed adverse events on the developing child. Proposed change (if any): Add late pregnancy loss	
142		Comment: There are some terminological inconsistences which are likely to make communication of safety information difficult. "Teratogenicity" is defined as causing birth defects in line 142 (separately from "pregnancy loss") but in line 160 a "teratogen" may cause pregnancy loss or birth defects and in line 258 a teratogen causes congenital abnormalities defined as structural birth defects. Proposed change (if any): Delete "teratogenicity" from line 142. Line 258: "that can cause foetal death, malformation, growth	

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		retardation or functional deficit".	
143		Comment: Replace 'on' with 'affecting'.	
144		Comment: Replace 'on' with 'affecting'.	
145		Comment: The wording currently could be understood to suggest that the impact of an exposure on the brain only occurs after organogenesis. Proposed change (if any): Suggest rewording to highlight the susceptibility of the brain throughout gestation and beyond into childhood; which has relevance for breastfeeding exposure.	
155		Comment: pulmonary hypertension and sedation are other potential (ir)reversible physiological impacts on the neonate that are worth to mention. Proposed change (if any): suggest adding, as these are somehow AE of special interest in this setting.	
169		Comment: 3% refers to major malformations. Proposed change (if any): change birth defect to major malformation or major anomaly	
172		Comment: "birth defects in general should not be studied as one single outcome" – agree this is very important Proposed change: none.	
178		Comment: It also means 'birth defects' in general should not be studied as one single outcome. Proposed change (if any): Needs additional clarification	
180		Comment: This section identifies that there may be immediate effects on the neonate from breastfeeding but	

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		does not consider that exposure to medications through breast milk conveys a prolonged period of exposure which may pose a risk to on-going brain development. Proposed change (if any): Suggest re wording to reflect the possibility of a potential impact on brain development from exposure to medicinal products through breastfeeding.	
186		Comment: The risk to the child can be different depending on whether the mother takes a single dose or a few doses, or is under chronic treatment with the medicine, and whether she took the medicine already during pregnancy or initiated treatment during breastfeeding. Proposed change (if any): Add age child	
193		Comment: It would be worth adding the terminology for paediatric ages or reference to ICHE11 and using them accordingly and appropriately throughout the document	
206		Comment: Whilst terminology with regards to birth defects is outlines there is no such glossary for neurodevelopmental outcomes. The consideration of neurodevelopmental outcomes has recently become more central in pregnancy pharmacovigilance and there is often a large misunderstanding about what this term refers to and the different aspects of brain functioning which fall under this umbrella term. Proposed change (if any): Suggest adding in a similar style of glossary for the most important neurodevelopmental outcomes.	

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207		Comment: "Pregnancy outcome" is defined here as including foetal death, termination or livebirth. However, "Adverse pregnancy outcomes" is a much wider term commonly used in pharmacovigilance (e.g. in line 300) to describe the entire range of outcomes from death to birth defects to delayed adverse effects. In line 344 and 860, it is unclear whether pregnancy outcome is solely survival. In line 602, pregnancy outcome is specified in the wider sense. Proposed change (if any): "Pregnancy Outcome" refers clinically to survival to birth (foetal death, termination, livebirth etc) but in common usage in surveillance and research "Adverse Pregnancy Outcomes" also refer more widely to foetal or perinatal deaths, congenital anomalies, and delayed development if potentially due to in utero exposures".	
210		Comment: We need to harmonize variation in definitions like this from different data sources, e.g.: 20 vs 22 weeks.	
212		Comment: Stillbirth is defined as after 24 weeks in the UK. Proposed change (if any): add to text	
212		Comment: Late foetal death (after 22 completed 212 weeks of gestation) is known as stillbirth. Proposed change (if any): Add stillbirth to the list of terms	
214		Comment: Refer to "spontaneous abortion" which is more specific than "miscarriage" and which in turn had to be explained further down.	

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214		Comment: Miscarriage: Spontaneous abortion and molar pregnancy. Proposed change (if any): Make 'molar pregnancy' a separate entity	
215		Comment: Reasons for "termination of pregnancy" should be defined as "1: non-medical, 2) medical, maternal indication, 3) medical, foetal anomaly." Note that Termination type "3" is often referred to as "TOPFA".	
215		Comment: No definition of termination of pregnancy for medical reason. Proposed change: Add this term in the definition section can support the analysis of induced abortion for medical reason (potential link to the medicinal product)	
219		Comment: There is confusion about the use of gestational age and date of "LMP". An alternative approach would be to estimate date of conception instead. The reporter could then choose between doing this by relating this to LMP or by basing it (or updating it) on ultrasound.	
224		Comment: Birth weight: Initial weight of the infant at birth. Proposed change (if any): Add in grams	
234		Comment: Should the distinction between IUGR & SGA be made? The preferred terms should be SGA which is measurable, rather than IUGR which requires more information about growth potential.	
244		Comment: Neonatal withdrawal is not confined to psychoactive substances. It is important following maternal	

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		corticosteroid or beta blocker exposure. Add to text.	
245		Comment: Definitions reported are not in line with EUROCAT definitions. Proposed change (if any): Adoption of the EUROCAT definitions already widely in use in 49 registries in 23 countries.	
250		Comment: These distinctions between "congenital anomaly", "congenital abnormality" and "congenital malformation" are not widely agreed/observed. Proposed change (if any): "Congenital anomaly, congenital abnormality and congenital malformation are often used synonymously to refer to structural birth defects. However, congenital anomaly and congenital abnormality can also refer more widely to functional and genetic diseases which do not involve structural birth defects, and congenital malformation may be used narrowly for errors in morphogenesis excluding disruptions or deformations. The term used must always be defined to avoid misunderstanding. In this GVP guidance, "congenital abnormality" will be the chosen term to refer to structural birth defects, whether due to errors of morphogenesis or disruption or deformation, and whether detected at birth or not.	
256		Comment: Multiple congenital abnormalities. Proposed Change: A concurrence of two or more different morphogenetic errors. Two congenital anomalies in the	

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		same baby may relate to the same morphogenetic error ("sequence") and the term should be reserved where possible for two or more morphogenetic errors.	
258		Comment: Teratogen: A medicine or other environmental factor that can cause congenital abnormalities. Proposed change (if any): Traditional abnormality or more up to data anomaly?	
261		Comment: In line 169 it was stated that around 3% had a birth defect. Proposed change (if any): Describe more uniformly	
274		Comment: This is not usual Total Prevalence rate definition. Proposed change: Total prevalence rate is number of cases among live births, stillbirths and terminations of pregnancy for a foetal anomaly divided by the Number of live births and Still births. It is important that terminations of pregnancy are not on the bottom line as in some places/populations the proportion of terminations compared to births is extremely high (e.g. as high as 25%). Most of these will be social terminations and many countries have very different reporting systems for such terminations, so the information is extremely difficult to obtain. Therefore, terminations in general are not included in the bottom line. It is important that terminations of pregnancy on the top line are distinguished as those having a foetal anomaly as early "social" terminations occur and some of these may	

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		have undiagnosed anomaly of interest which we have not been able to look for as the terminations are so early so counting TOPFAs indicates that these terminations are cases in which the presence of a foetal anomaly has been looked for.	
275		Proposed change (if any): Add terms for maternal and neonatal death	
302		Comment: "The background rates of adverse pregnancy outcomes in the target populations may need to be specified in the RMP". This may not always be practical since an unmedicated population may not be available or comparable, and relative rather than absolute measures may be more appropriate to take into account differences between population in outcome measurement. The same problem recurs in line 471. Proposed change: "Given that such specific underlying conditions may be the indication for prescribing, measures to distinguish the effect of the medication from that of the underlying condition must be specified in the RMP, together with existing knowledge on the effect of the underlying condition on pregnancy outcome". Line 471: "taking into account the impact of the underlying maternal condition (i.e. non-exposed disease comparison group or other method to analyse confounding by indication) and other potential confounders.	
314		Comment: Spontaneous reporting rates of pregnant /	

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		lactating women are relatively low. More information is likely received from organized data collection schemes (e.g., national pregnancy registries). In addition, the collection of data from pregnant / lactating women where no AEs are observed would provide contextualizing information, but these instances are unlikely to be re reported by HCPs if there is not an accompanying AE. Proposed Change (If any): Spontaneous reporting, together with organized data collection schemes such as national pregnancy registries during the post-authorisation phase is one are the primary sources of information on the uses of products during pregnancy and of adverse reactions occurring following exposure in utero or during breastfeeding	
317		Comment: And/or the suspected medical product was taken by the father. Proposed change (if any): In the ICH-e2b-R3 format Route of administration there is no option to indicate that the father might be the source of the drug exposure of the embryo/foetus (for maternal transmission this is available in the trans placental and trans mammary options).	
320		Comment: This paragraph makes clear reference to exposure during pregnancy and breastfeeding. However, Appendix 1 speaks only about EDP. Recommend specifying in an additional appendix what must be done for	

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		breastfeeding.	
333		Comment: For foetal cases, it is indicated to use the MedDRA term 'exposure in utero' which is different from the recommendation made in the last version of MedDRA PTC v.22.1 (Sept. 2019), that indicates to use "Maternal exposure during pregnancy" or "Paternal drug exposure before pregnancy". Recommend to make the wording more generic – see in red. Proposed Change: For the route of administration, code, in the case of exposure in pregnancy leading to pregnancy loss or other adverse pregnancy outcomes, the route of administration as 'transplacental' and use the most appropriate MedDRA term indicating the exposure 'exposure in utero' in the Reaction/event section;	
335		Comment: Consider using the MedDRA term "Maternal exposure during pregnancy" in the reaction/event section, instead of 'Exposure in utero'.	
349		Comment: Unsure of meaning. Is this 'as possible' or 'as can possibly be obtained'?	
349		Comment: As many specific data elements as are possible to be obtained should be included. Proposed change (if any): Seems logic, wouldn't it be better to also include minimal requirements.	
353		Comment: Prospective cases should be followed up and reported even regardless of how the pregnancy ended and regardless of whether an anomaly in the offspring was	

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		noted.	
355		Comment: The current wording here describes studies or spontaneous reports as 'prospective' only if recruited prior to ultrasound. This is very much biased towards structural malformations. For important functional outcomes such as neurodevelopment or child health, recruitment at any time up to the end of pregnancy would be considered 'prospective' as the outcome of interest is not yet known. Proposed change (if any): Suggest additional wording noting that prospective enrolment may be classed differently for different child and maternal outcomes.	
363		Comment: Requesting simply "gestational age at time of exposure" is too ambiguous. Full gestational timing of exposure to medication is needed including earliest and latest age. Ideally, full dates (those relevant to the pregnancy) of LMP, start and stop dates of medication should be provided.	
365		Comment: Provided in months, weeks, days or trimester. Proposed change (if any): Remove trimester, this is not specific enough.	
374		Comment: The dates and findings are important too.	
379		Comment: Table P does not include any examples of where functional or longer-term outcomes are being reported. Proposed change (if any): Suggest additional example and reformatting of the table to include a wider variety of	

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		outcome examples.	
379		Comment: Requirements for the submission of individual case safety reports with pregnancy exposure. For the particular situation of twins, the document specifies "1 case for each twin with an adverse reaction, the individual case should be linked". It does not specify if there should be a mother case as well and if that should be linked to the twin cases.	
379		Comment: In table P III.1 and in footnote 7, it is mentioned no ICSR is required when there is no adverse reaction in mother and no adverse reaction in child. However, the absence of adverse reactions in pregnancy or lactation is very valuable information. The reactions may be coded using MedDRA LLT's "Normal pregnancy" and "Normal newborn". Please clarify whether this course of action is allowed, even though it is not a requirement.	
379		Comment: Table PIII.1. Terminology does not correspond to the terminology defined in the guidelines and are not mutually exclusive. Proposed change: Produce definitions for terms used, or harmonise.	
379		Comment: Need to have the same requirements for exposure through breast feeding. Proposed change: Produce the same level of guidance for breast feeding exposure.	
390		Comment: The source of exposure information should be	

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		clearly distinguishable.	
394		Comment: Please consider changing exposure calculation should be provided to "shall be provided when available" as this data is not available for all products	
417		Comment: Specific drug related risks may also apply to the pregnant woman/mother – not only to the foetus/child. Proposed change (if any): Suggest including "pregnant women" in the sentence "specific risks to the embryo, foetus or child"	
418		Comment: There is an opportunity here to highlight that the investigation of teratogenic outcomes should now be wider than that of major structural malformations. Proposed change (if any): Suggest additional wording highlighting the central importance of other outcomes (including neurodevelopment and child health).	
443		Comment: In this situation the term child is accurate; if the FU is from 2 years onwards, but neonate/infant should be added if the FU includes ages from birth to 2 years	
451		Pharmacokinetic data in human pregnancy is challenging but should be prioritised. However, estimates based on known parameters should be recommended e.g. metaboliser distribution, Vd	
451		Comment: The suggestion to monitor free rather than total maternal concentrations makes sense, but would suggest to change the wording to also include data obtained by	

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		recalculating the free concentration based on known physiological changes, in particular the decreased albumin levels during pregnancy. Currently, the perception may exist that these free levels can only be obtained by performing measurements in plasma samples obtained from pregnant women. However, for albumin-bound drugs, reliable calculations can be used based on total maternal concentrations along with plasma protein binding characteristics of the specific medicine. Proposed change (if any): sometimes, it is suggested that free rather than total medicine plasma levels are taken into account in pregnant women. This can be achieved either by experimentally determining the free concentration in maternal plasma samples, or by calculating a pregnancy-relevant value for the free fraction based on knowledge of changed albumin concentrations during pregnancy and medicine-specific albumin binding parameters.	
457		Comment: The examples of diabetes and asthma treatment given in paragraph PIIIB4.1 for pharmacokinetic studies are surprising: blood concentrations of these medications are not routinely evaluated. Blood glucose (and not the blood-level of the drug) is measured for diabetic patients. A good control of the disease is needed in these 2 examples, but it is not with a pharmacokinetic approach. Neuro psychotropic drugs are better examples, such as lamotrigine.	

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466		Proposed change: Replace with 'lactation'	
472		Comment: Mention the importance of including a comparator group	
475		Comment: This is a very loose requirement for pregnancy safety studies which could lead to delay in providing safety evidence. Proposed change: At the time of marketing authorisation, a drug utilisation study in pregnancy must be foreseen, and a phased plan of implementation of medicine safety studies for pregnancy as exposure numbers increase over time.	
482		Comment: It should be made clearer as to who and how it is decided that additional PASS studies, beyond simply drug utilisation, are required. Further some discussion about who is best placed to undertake these studies would be useful. Proposed change (if any): Suggest additional wording to provide clarity.	
489		Comment: "Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.III.A.1.3.), it is usually necessary to include participants from more than one country in order to achieve adequate power." Proposed change (if any): Suggest recognizing the situation in the guideline that when exposure to a medicine is extremely low, it is possible that including participants from multiple countries would still not be able to achieve adequate power.	

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490		Comment: It is currently stated that due to the rarity of outcomes, studies 'across different countries are likely'. This is certainly the case for rare outcomes such as specific types of structural defects, however in more commonly observed outcomes, which are investigated with sensitive measures, smaller cohorts from a single country can provide adequately powered cohorts. Proposed change (if any): The current wording surrounds rare outcomes such as specific birth defects but should be modified to reflect that different outcomes are likely to require different approaches both in terms of methodology and cohort sample size.	Keep
492		Comment: The well-known limitations to pregnancy registries (limited statistical power for specific risks such as specific major congenital malformations, challenges related to patient recruitment and retention etc) should be highlighted in this section.	
499		Comment: Could specific examples be given of those exceptional cases where product-specific pregnancy registries may be appropriate?	
507		Comment: Electronic records need to be 'combined with congenital anomaly registers	
520		Comment: Asking women to assess their own infants is potentially problematic. Proposed change: Professional assessment is also needed.	
527		Comment: This section reads as though longer term	

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		outcome studies will be an optional extra to PASS studies looking at teratogenic risk and suggests that structural malformations will remain as the central feature in risk identification. This goes against what we know about how teratogens impact on the development of the fetus and the varied yet important outcomes which can be produced. The substantial life time impact of certain child health and neurodevelopmental functioning highlights the significance of ensuring that non-structural endpoints are also considered. Proposed change (if any): Suggest additional wording regarding the importance of these outcomes and in what situations longer term outcome studies must be completed (i.e. when there is an identified structural malformation risk, when another drug in that class is implicated as altering foetal brain development).	
527		Comment: Be careful not to restrict to neurodevelopmental outcomes e.g. diethylstilbestrol example. Proposed change: Only refer to neurodevelopmental outcomes as examples of long-term outcomes.	
536		Comment: Long-term outcomes should include school performance	
540		Comment: A pharmacologist could be added to the list	
546		Comment: Substance misuse should be included	
556		Comment: This paragraph is unclear. "Self-controlled designs and positive and negative controls "should be	

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		described in more detail. Proposed change (if any): We assume negative controls are comparing women with exposures in the relevant gestational time period to women with exposures only before but not during pregnancy or women with exposures during pregnancy, but not the specific gestational time periods of interest. It is unclear what a positive control is. The sentence These designs may not always be appropriate …. with a very long half-life, we assume refers to using the negative controls described above, but not necessarily the other suggestions in the sentence	
568		Comment: Should this bullet explicitly include age post-partum, for those endpoints which only become apparent with post-natal developmental Proposed: which pregnancy outcomes and outcomes and at what age in the child will be evaluated	
572		Comment: Is "common" an appropriate term? The use of the medicinal product is based on the medical need of the mother and not on the basis that she is breastfeeding. Proposed: In cases where no human data are available on the extent of medicine transfer into breast milk, where use by breastfeeding women is expected to be common difficult or unable to be avoided, due to the medical needs of the mother……	
572		Comment: Suggest specifying here that next to clinical	

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		lactation studies also PBPK studies in lactating women should be conducted. This is in line with the general comment mad above. Proposed change (if any): Would add a separate second paragraph from line 579 onwards: While more clinical data regarding the extent of medicine transfer to breast milk will become available, the parallel development, validation and application of PBPK models for the lactating state should be encouraged. As these PBPK models can take into account both lactation-specific physiological descriptors and medicine-specific disposition data, they carry promise in predicting exposure (including milk transfer) to medicines for which clinical data are lacking and/or challenging to obtain. In addition, the construction of linked maternal and infant PBPK models should be considered. The existing experience with infant PBPK models for orally administered medicines in this population can be used as a solid starting point.	
579		Comment: Medicine concentration levels in breast milk samples should be measured and a relative infant dose Calculated. Proposed change (if any): Add bases on AUC (not only single measurements)	
579		Comment: Colostrum should be included, and pharmacokinetic parameters and effective doses are different in pre-term neonates.	
582		Comment: The impact of medicines on initiation and	

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		establishment of breastfeeding is not mentioned: add 'initiation and' to line	
594		Comment: A more detailed approach for detecting potential safety signals in spontaneous reports is missing. Given the focus on data collection, a separate paragraph on the detection of safety signals is advisable.	
616		Comment: Risk minimisation should include intensified efforts to ensure appropriate prescribing in women of childbearing age, according to clinical guidelines of the country, to avoid unnecessary exposure. Proposed change: Add "Risk minimisation should include intensified educational efforts to ensure appropriate prescribing in women of childbearing age, according to clinical guidelines of the country, to avoid unnecessary exposure."	
633		Comment: Replace 'becoming aware of' with 'raising awareness'	
666		Comment: Risk minimisation may not be limited to avoiding exposure in utero and during breastfeeding. Well considered risk minimisation may result in continuing use of the medication by the mother, when the risk of discontinuation or switching outweighs the (limited) risk of continuation. For instance: Poor treatment of chronic maternal disease may result in increased risk of IUGR or preterm birth. And the benefits of breastfeeding outweigh the risks of the exposure of the infant (if any) for most drugs.	

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689		Comment: Need to add initiation, establishment, and duration to production.	
761		Comment: Absence of data should be added to the PSUR.	
768		Comment: An explanation of what is meant by "proportional prevalence" should be given.	
770		Comment: "Before conception" must be defined. This should be done in relation to the ½ life of the medicine.	
770		Comment: "Elective" termination usually implies a non-medical reason for termination. Replace this term with "induced" termination. Distinguish here between three types of induced termination: non-medical, medical (maternal indication), medical (foetal anomaly).	
770		Comment: What does "timing" mean? Is this the start of exposure, the end of exposure, or any exposure meaning that cases could contribute to more than one timing category? If categories are to be considered non-overlapping, replace these by "At least 1st trimester" (see text also in line 765), "before conception only", "only after 1st trimester". "during all pregnancy" can be very misleading meaning different things for full-term pregnancies and for those terminating early; remove this column. State clearly that "Unknown" must apply to cases which are known to have exposure in pregnancy but for which the exact timing is unknown.	
770		Comment: Table PIII.2. Clarify how to fill in the table if	

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		exposure of a single case occurs across multiple time periods. Moreover, what is the definition of "congenital anomaly" being used here in relation to the terminology as defined in these guidelines?	
770		Elective termination (no foetal defects or unknown) is not discussed elsewhere in the document and should be contextualized in terms of why the information should be collected, considering all terminations should be authorised by a one or more HCPs and many terminations will be independent of any the presence or absence of any therapeutic regime the mother is undergoing.	
800		Comment: Further specification might be of value; knowing the method of data collection (medical records, interview, online questionnaire etc)	
809		Comment: Does "weight" refer to current weight or pre-pregnancy weight? Please specify. Also specify units the measurements should be given in.	
811		Comment: Should date of previous pregnancies be included?	
824		Comment: Specify that this is the first day of last menstrual period.	
826		Comment: Collect first and last gestational age of exposure to drug.	
844		Comment: Questionnaire should include medicines in labour, birth centile, breastfeeding initiation, time point for	

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)*
		breastfeeding, and interactions with oral contraceptives.	
860		Comment: Align this with the terminology used in the table at 770. Avoid terms: "miscarriage", "elective", "late foetal death".	
868		Comment: Specify major or minor, specify if of genetic/chromosomal origin.	
879		Align this with the terminology used in the table at 770. Avoid terms: "miscarriage", "elective", "late foetal death".	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
IQVIA [redacted]

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	We recommend providing more guidance on the use of secondary data sources to conduct safety studies in pregnancy. Outcome misclassification is a serious threat to study validity when using secondary sources of data. The misclassification of a single rare event can significantly impact study results. Given that results from validation studies of specific congenital malformations have varied widely, further guidance on outcome ascertainment efforts and validation or adjudication of outcomes in secondary data is warranted.	
	We were encouraged to see the inclusion of a subsection of long-term pregnancy outcomes in the guidance. Further discussion of the clinical relevance of scales used to measure neurodevelopment outcomes would be helpful to researchers conducting studies in this emerging field.	
	We noted that there was a higher emphasis on lactation data in the body of the guidance than is recommended for data collection in the Appendix, consider adding some variables for lactation-specific research questions.	

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)*
Line 81		Comment: In spontaneous reporting, "adverse event" is not synonymous to "adverse reaction" as the first does not imply an implicit suspected causality and the second does. Proposed change (if any):Change to "In spontaneous reporting~~, the term 'adverse event' is synonym to (suspected) adverse reaction and~~ all birth defects are (suspected) 'serious adverse reactions'	
Line 107		Comment: This section refers only to the data available at the time of marketing authorization. We recommend changing the title of the section to specify "availability and interpretation of data at the time of marketing authorization". We also recommend including information on the availability on safety data after the time of marketing authorization and the limitations for its interpretation. For example, pharmacovigilance data usually uses spontaneous safety reporting which is prone to under-reporting, incomplete information, or having no denominator.	
Lines 106 to 124		Comment: We suggest mentioning that when there is not enough information to estimate if there are potential risks	

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)*
		of teratogenic effects and the use of the medicine among pregnant women is likely to occur, then exposure during pregnancy should be considered a safety concern (missing information) and actions be in place to monitor the use in such population. The same recommendation applies for breastfeeding.	
Lines 132-134		Comment: We recommend acknowledging that a greater association between use of a medication during pregnancy and adverse outcomes, may result in a lower prevalence of use during pregnancy since we would expect that these products would include risk minimisation measures in the label to prevent pregnancy.	
Lines 142-143		Comment: Adverse event should be replaced by Adverse reaction because the sentence implies a negative consequence of exposure (so there is an implicit causal attribution). Proposed change (if any): Replace "adverse event" by "adverse reaction"	
Lines 169-179		Comment: Further detail regarding feasibility issues with powering a study around an outcome of a specific malformation versus "total malformations" (as we see in most registries) would be helpful. Specific discussion on	

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)*
		the limited interpretation of aggregated endpoints (e.g., congenital malformations) would strengthen this section.	
Line 234		Comment: We recommend adding small for gestational age (SGA) as an outcome of interest. IUGR and SGA are different outcomes and can be present independently. See Beune et al 2018 (https://www.ncbi.nlm.nih.gov/pubmed?term=29499988)	
Line 286		Comment: Consider adding partner in sentence "For products with anticipated use in women of childbearing potential there is a need to reflect…" Proposed change (if any): "For products with anticipated use in women of childbearing potential or their partners there is a need to reflect…"	
Line 292/293		Comment: We recommend rephrasing to align with terminology in GVP V: "For all three categories of safety concerns, recognition in the summary of safety specifications usually implies….". As an alternative for summary of safety concerns, the term safety specification could be used. Proposed change (if any):"For all three categories of safety concerns, inclusion in the summary of safety concerns	

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)*
		usually implies…."	
Line 379		Comment: Consider adding in the possibility of a case related to the father, in line with GVP VI.	
Line 381		Comment: We suggest making it more explicit in the section on the PSUR that relevant data here also include reports of (maternal or paternal) exposure during pregnancy not resulting in adverse reactions in mother and/or foetus or baby (in line with table at line 379).	
Line 412-414		Comment: We suggest a clarification in this section that additional pharmacovigilance activities are required in the cases where safety data are limited but also if there are concerns that exposure will be likely (i.e. if use in pregnant women is considered to be a safety concern). Proposed change (if any): "For medicines where safety data relating to use of a medicine in pregnancy and breastfeeding are limited <u>and exposure in pregnancy or adverse pregnancy outcomes are considered safety concerns</u>, additional pharmacovigilance activities may be warranted"	
Line 474		Comment: We recommend adding a reference to the section where RMMs are detailed (P.III.B.7).	

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)*
Line 484		Comment: Suggest to change ", or" to ", and" as in general it would be the combination of the different types of data listed that would lead the decision on performance of further studies.	
Line 499		Comment: The guidance notes that "in exceptional cases, a medicinal product-specific pregnancy registry may be appropriate", in practice, we have observed more examples of product-specific registries than disease-specific registries. It would be helpful if the EMA could clarify what "exceptional cases" would be.	
Line 504		Comment: Although the use of a hybrid approach has multiple advantages we recommend adding an emphasis on avoiding double counting across the data sources.	
Line 516		Comment: Please specify whether retrospective data may also be considered for childhood outcomes.	
Line 563		Comment: It would be helpful to note the potential for exposure misclassification due to inaccuracies in recall of LMP as well as the analysis of "pregnancy" exposures that end during the period between LMP and LMP+14.	
Line 738		Comment: Consider amending to mention that in the case	

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)*
		of a highly teratogenic substance, both male and female contraception would be recommended.	
Line 809		Comment: Please specify whether weight measurement is pre-pregnancy or during pregnancy.	
Line 837		Comment: Consider using the term "recreational or illicit drugs" as legality of drugs may be country-specific.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

February 26th, 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
International Society of Pharmacovigilance - ISoP Special Interest Group Women's Medicines

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement *and* *https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	It is recommended to use the correct pair of terms 'benefit-harm' instead of the pair of terms 'benefit-risk' (or 'risk-benefit') throughout the whole document.	

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)*
45		Comment: Unclear whether it is 'widely recognised' that there is a need for guidance Proposed change (if any): For clarity this should say widely recognised by whom.	
46		Comment: Although pregnant and breast feeding women are considered 'vulnerable' traditionally, attitudes have changed. This is an ethical not a regulatory issue so guidance must be careful not to imply that this is a rigid regulatory opinion. Proposed change (if any):	
53		Comment: Are there any authorised medicines that are known to benefit the unborn child? Sentence implies there are. Proposed change (if any):	
62		Comment: 'Safety data … pre-authorisation are limited' is out of tradition. The sentence implies that this is regulatory expectation that there needs to be 'restrictions'. Should this guidance apply across the lifecycle of a medicinal product including in clinical trials? Proposed change (if any):	

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)*
66		Comment: '...and to identify and characterise risks is important...' Proposed change (if any): insert 'and mitigate' in the sentence: '...and to identify, characterise **and mitigate** risks is important...'	
81		Comment: The term adverse event is NOT synonymous with ADR. Although all ADRs are AEs, all AEs are definitely not ADRs especially in pregnancy cases. Is this what is being implied that an AE in a pregnant woman should always be regarded as a suspected ADR?	
117		Comment: Exposure through semen should be dealt with in a stand-alone paragraph. Should this always be a potential risk if clinical risk is unknown? If so, guidance should advise so.	
134		Comment: When it says 'advise not to use', do you mean a contraindication or a warning? Either way, this can still be studied such as in a PASS. Current wording in such a way could discourage collection.	
147 - 150		Comment: The definition of organogenesis is not correct. This most sensitive time for the development of malformations covers the period from the beginning of the 3rd week till the end of	

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		the 8th week after fertilization, or gestational weeks 4-10 counting from the last menstrual period [See Moore et al. The Developing Human: Clinically Oriented Embryology, 11th Ed 2020 p 451, Fig 20.18, p 434 Fig 20.1]. To include the development of genital organs and for practical reasons, the first trimester is most often defined as the first 13 weeks (until week 12 6/7) from the last menstrual period. If organogenesis remains as defined here, namely until GW 16 after LMP, this can result in an underestimation of the birth defect rate in studies with non-continuous drug exposure. This definition also contradicts what is said further down the text (line 199).	
160 - 161		Comment: 'Stillbirth' refers to death after week 22. Would 'foetal death' be more appropriate here? Proposed change (if any): Delete 'stillbirth' and insert instead 'foetal death'	
214		Comment: Molar pregnancy or hydatidiform mole are very specific conditions and so would be better separated out.	
258		Comment: Will or should the GVP Guideline advise what 'other environmental factors' should be considered?	
331 / 335		Comment: In line 335 a MedDRA term "exposure in utero' is	

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)*
		mentioned. This is not an exact MedDRA term and may confuse the readers. In our view, more guidance is needed here. This becomes clear when looking at the numerous Preferred Terms (PTs) that are available for coding of scenarios of exposure during pregnancy and exposure in utero. The terminology clearly differentiates drug exposure in pregnancy and drug exposure in utero with the following PTs: • Maternal exposure before pregnancy, maternal exposure during pregnancy, maternal exposure timing unspecified and maternal exposure during delivery are to be used when it is known that the **mother was exposed** to a medicinal product. • PTs Paternal exposure before pregnancy, Paternal exposure during pregnancy and Paternal exposure timing unspecified are to be used when it is known that the **father was exposed** to a medicinal product. • PTs Drug exposure before pregnancy and Exposure during pregnancy are to be used when confronted with an **unspecified 'exposure'**, i.e. when it is not clear whether the father or the mother suffered an 'exposure'. • In addition, there are PTs for **exposure in utero** (PT Foetal exposure during pregnancy, PT Foetal exposure timing unspecified, PT Foetal exposure during delivery) and one for exposure in utero via father (PT Exposure via father). • And last but not least, additional PTs exist for capturing **exposure during breastfeeding/ via**	

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)*
		breast milk (PT Maternal exposure during breast feeding and PT Exposure via breast milk). PTs for exposures in utero should only be used when it is suspected or known that a medicinal product can cross/ has crossed the placenta. The PtC document for MedDRA Term Selection is not very specific in this regard, so that the reference in line 331 is not truly helpful. If the agency would like to see a clear differentiation of all scenarios of exposures during pregnancy and exposures in utero, then they should either ask for an amendment of the PtC document or provide more specific guidance on how to differentiate the relevant scenarios via MedDRA coding in the GVP guidance document itself.	
386 - 389		Comment: Proposed change (if any): 'The PSUR needs to summarise the relevant safety information from spontaneous ICSRs of adverse pregnancy outcomes, or adverse reactions/outcomes **in the mother during pregnancy** and in the child following exposure in utero or during breastfeeding, ICSRs published in the medical literature and post-authorisation studies (PASS) ongoing or finalised during the reporting interval'	
424 - 426		Comment: Please be explicit what is meant by 'relatively uncomplicated' during breastfeeding compared to during pregnancy so that the reader does not have to guess.	
572 - 575		Comment:	

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)*
		What is meant by 'common' in this context? Does this refer to authorised indication(s) or normal and frequent use of the product? Please specify what is meant.	
722 - 740		Comment: In a separate sub-paragraph it would be worth including that some herbal medicinal products, such as extracts of St. John's wort (Hypericum perforatum L.) may reduce the effectiveness of certain contraceptive interventions. In such situations it is advisable to use alternative effective contraceptive methods.	
766 - 767		Comment: Does the wording mean that all functional anomalies are AEs/ADRs? Leave wording so, if that is what is meant.	
770 – Table PIII.2		Comment: Is the term 'stillbirth' correct or should this be the broader term 'foetal death'? The broader term is suggested/recommended.	
780 - 781		Change wording: 'Reliable information regarding patient exposure in breastfeeding is not routinely available but may exist in **some birth cohorts in EU member States.**'	
831 - 832		Comment: Exposure to products does not specifically mention complementary/alternative remedies/medicines/natural health products/dietary supplements, including herbal and other traditional medicines etc., including where accessed through a 'natural-health'/traditional medicine practitioner	

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833		Comment: The information requested on products of exposure includes "Name" but the type of name is not specified. Ideally, proprietary name, drug name, and manufacturer should be requested. This is especially important for herbals and related products so that the specific manufacturer's product can be identified.	
837		Comment: 'Use of' also needs to specifically mention vaping products, and cannabis and cannabinoid products. Proposed change (if any): 'Use of tobacco, alcohol, illicit drugs (specify amount and if stopped during pregnancy), **vaping products, cannabis and cannabinoid products**'	
855		Comment: 'Medical products exposure': Is there any difference to what is requested in lines 831 – 832 and 837?	
902 – Table rows 'highly effective		Comment: In the table it refers to 1) 'typical use failure rates of less than' and …'greater than 1%' as well advising barrier	

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methods' and 'effective methods'		methods during use of some teratogen products/substances. Are both points consistent with or present within authorised SPCs for such products?	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation: International Society for Pharmacoepidemiology: Medications in Pregnancy and Lactation Special Interest Group
Name of individual: Compiled by [redacted]

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Thanks for updating this guideline. The draft is very clear. This is a very interesting and useful document. The emphasis on not grouping birth defects into one category is very welcome. Some further clarity needed as to the range of methods that may be needed to account for confounding by indication for treatment, as a suitable unexposed disease comparator may not be feasible. Risk minimisation should include efforts to ensure appropriate prescribing, avoiding unnecessary exposure. Some terminological confusion needs to be attended to.	
	Is an update "from data to labelling" planned?	

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)*
53-54		Comment: The meaning of the parenthetical text is unclear (i.e., referring to the foetus, the child, or both? Proposed change: remove parentheses. Consider replacing "unborn child" with "foetus" or "foetus or child".	
62		Suggest adding "Pregnancy exposure data obtained….": in place of "Safety data obtained…"	
64		Comment: "Safety data for special populations are even more limited". The comparison in this sentence is unclear, given that the first paragraph states that pregnant and breastfeeding women are considered special populations: who is being compared with whom? Proposed change: please clarify	
71		Comment: This sentence could be reworded for clarity	
73		Comment: "the guiding principle is …". Please clarify: the guiding principle for what?	
73, 616-665		Comment: "well-informed about uncertainties" – agree this is very important. However, communication of uncertainties does not appear in lines 616-665. Proposed change: Include communication of uncertainties in PIIIB6.	

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)*
140-141		Comment: "from the last menstrual period" should be "from the first day of the last menstrual period". This should be specified at least once in the document. "Clinically, gestational age is usually calculated from the last menstrual period, but more accurately established from ultrasound diagnostics". It would be important to say here what the time zero for gestational age is when estimated via ultrasound: is it conception, or LMP, any other?	
142,160, 258		Comment: Inconsistencies in terminology are likely to make communication of safety information difficult. "Teratogenicity" is defined as causing birth defects (line 142), separately from "pregnancy loss". In line 160, a "teratogen" may cause pregnancy loss or birth defects. In line 258, a teratogen causes congenital abnormalities defined as structural birth defects. Proposed change: Delete "teratogenicity" from line 142. Line 258: "that can cause foetal death, malformation, growth retardation or functional deficit"	
143		Comment: "developing child". Proposed change: Consider dropping "developing".	
145 and later		Comment: Please indicate time zero for the listed gestational ages (e.g., LMP) and clarify the overlap (e.g., are the listed bounds are included; e.g., for weeks 0 to 4, are weeks 0 and 4 included? Note that week 4 is also mentioned in the following gestational age category, 4-16, and so on with week 16.	
155-156		Comment: Timing needs to be defined in "late pregnancy". In the other groups, timing of exposure is clearly defined (e.g., gestational week 0-4) but not in "late pregnancy". It is not clear if late pregnancy refers to second and third trimester or only third trimester. What is the reference for such a division of gestational weeks? It is not consistent with the terminology used later in the document. In the paragraph "late pregnancy and during delivery ", the potential effects of drugs used at delivery could be added.	

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)*
		Proposed change: add consistency; add definition of timing in brackets after late pregnancy, i.e., Late pregnancy *(since week X to delivery)* or during delivery.	
162, 440, 480, 552		Comment: "Endpoint" is terminology typically used in clinical trials but not in non-interventional studies. Proposed change: Replace the term "endpoints" for "outcomes".	
164		Consider another verb beside "perturbed" such as "disturbed" or something else.	
169		Comment: Reference(s) is missing to support "Overall, birth defects that are visible at birth are relatively frequent at around ~3% of all live births". Proposed change: Add reference(s) after the statement "Overall, birth defects that are visible at birth are relatively frequent at around ~3% of all live births *(ref)*"	
170-171		Comment: A reference(s) is missing to support "…(and has been reported as as 170 ranging from 1 in 700 to 1 in 30 000 live births, or less)" Proposed change: To add a reference(s) after the statement "…(and has been reported as as 170 ranging from 1 in 700 to 1 in 30 000 live births, or less) *(ref)*"	
171		Please add which malformations these examples represent	
172, 178		Comment: "birth defects in general should not be studied as one single outcome" – agree this is very important Proposed change: none.	

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)*
192 and later, P.III.A.2. Terminology		Comment: Please consider defining what retrospective pregnancy and a prospective pregnancy are in relation to enrolment in pregnancy registries, for table P.III.2, and for P.III. Appendix 1: Questionnaire to collect information on 786 pregnancy exposure (section A). One usual definition is related to the pregnancy outcome being known, but this definition does not take into consideration the information that pregnant women obtain during pregnancy (e.g., foetal malformations identified through prenatal ultrasound)	
199		Comment: Same remark concerning the reference to be added: for some embryologists, the organ-forming-period (with a high sensitivity to teratogens) begins at day 13 post conception.	
207, 300, 344, 602, 860		Comment: "Pregnancy outcome" is defined here as including foetal death, termination, or livebirth. However, "Adverse pregnancy outcomes" is a much wider term commonly used in pharmacovigilance (e.g. in line 300) to describe the entire range of outcomes from death to birth defects to delayed adverse effects. In line 344 and 860, it is unclear whether pregnancy outcome is solely survival. In line 602, pregnancy outcome is specified in the wider sense. Proposed change: "Pregnancy Outcome" refers clinically to survival to birth (foetal death, termination, livebirth etc) but in common usage in surveillance and research "Adverse Pregnancy Outcomes" also refer more widely to foetal or perinatal deaths, congenital anomalies, and delayed development if potentially due to in utero exposures".	
211		Comment: A foetal loss at exactly 22 weeks is not accounted for. Do you mean before 22 weeks and 22 weeks or later?	
246, 250, 253		Comment: These distinctions between "congenital anomaly", "congenital abnormality" and "congenital malformation" are not widely agreed/observed.	

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)*
		Proposed change: "Congenital anomaly, congenital abnormality and congenital malformation are often used synonymously to refer to structural birth defects. However, congenital anomaly and congenital abnormality can also refer more widely to functional and genetic diseases which do not involve structural birth defects, and congenital malformation may be used narrowly for errors in morphogenesis excluding disruptions or deformations. The term used must always be defined to avoid misunderstanding. In this GVP guidance, "congenital anomaly" will be the chosen term and follow EUROCAT definitions.	
256		Comment: Multiple congenital abnormalities. Proposed Change: A concurrence of two or more different morphogenetic errors. Two congenital anomalies in the same baby may relate to the same morphogenetic error ("sequence") and the term should be reserved where possible for two or more morphogenetic errors.	
264		Comment: The proposed calculation of the prevalence does not clarify how to account for multiple gestation (more than one foetus in same pregnancy event). Indicate that minor anomalies are not included. Proposed change: Specify how to account for multiple gestation in the calculation of prevalence.	
270-274		Comment: Not clear if the recommendation of the guidance is to include and present the 3 types of prevalence calculations (Live birth prevalence rate, Birth prevalence rate, Total prevalence rate) or to select one, or more than one of the 3, according to the study. Proposed change: To add clarification of the need to include and present all prevalence calculations. Otherwise, to clarify the use of each of the measures.	

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)*
302-303, 471		Comment "the background rates of adverse pregnancy outcomes in the target populations may need to be specified in the RMP". This may not always be practical since an unmedicated population may not be available or comparable, and relative rather than absolute measures may be more appropriate to take into account differences between population in outcome measurement. The same problem recurs in line 471. Proposed change: "Given that such specific underlying conditions may be the indication for prescribing, measures to distinguish the effect of the medication from that of the underlying condition must be specified in the RMP, together with existing knowledge on the effect of the underlying condition on pregnancy outcome". Line 471: "taking into account the impact of the underlying maternal condition (i.e. non-exposed disease comparison group or other method to analyse confounding by indication) and other potential confounders.	
366		Comment: Should the time zero for the reported gestational age be specified? e.g., "12 postconceptional completed weeks (ultrasound-based estimate)"	
379		Comment: Table PIII.1. Terminology does not correspond to the terminology defined in the guidelines and are not mutually exclusive. Proposed change: Produce definitions for terms used or harmonise.	
416		Comment: "A PASS may constitute a drug utilisation study, or it may investigate specific risks to the embryo, foetus or child." Suggest adding "A PASS may constitute a drug utilisation study or other types of studies designed to investigate specific risks to the pregnant women, embryo, foetus or child."	
443		Comment: should "additive" be "additional"?	

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)*
444		Comment: In the text "for a long enough period", what is considered long enough lacks definition; concrete information about what is considered long enough by type of study outcome would be useful because it has operational implications in studies. Proposed change: To add as guidance, definition of period of follow-up by type of outcome.	
447		Comment: In the statement "Inclusion of pregnant women in a PASS should be solely subject to the clinical decision to treat the woman for her medical condition." The information provided is only applicable to studies based on primary use of data such as pregnancy registries. However, pregnancy studies can be based on secondary use of data (data sources, registers) in which data is only extracted and treatment decisions have been taken prior to the study, independently of the study. This sentence is confusing as written. Proposed change: To specify in the guideline that the statement makes reference to primary use of data as follows: "Inclusion of pregnant women in a <u>prospective, observational</u> PASS should occur only after ~~be solely subject to~~ the clinical decision to treat the woman for her medical condition has been made."	
457		Comment: the examples of diabetes and asthma treatment given in paragraph PIIIB4.1 for pharmacokinetic (PK) studies are surprising: blood concentrations of these medications are not routinely evaluated; rather blood glucose is measured for diabetic patients. A good control of the disease is needed in these 2 examples, but it is not with a PK approach. Neuro-psychotropic drugs are better examples, such as lamotrigine.	
466		Comment: Typo: "pregnancy" should be "pregnant".	

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)*
475-486		Comment: This is a very loose requirement for pregnancy safety studies which could lead to delay in providing safety evidence. Proposed change: At the time of marketing authorisation, a drug utilisation study in pregnancy must be foreseen, and a phased plan of implementation of medicine safety studies for pregnancy as exposure numbers increase over time.	
491		Comment: "it is usually necessary to include participants from more than one country in order to achieve adequate power." Please consider adding at the end of the sentence "... adequate power or precision", as often, in observational studies, the study size is estimated based on the desired precision of the estimated measure of effect.	
501		Comment: Please consider the underlined addition: "facilitate the inclusion of internal comparator groups".	
522		Comment: "Information regarding the existence of a pregnancy follow-up activity should be included in any mandated pregnancy-related educational materials": materials related to risk-minimization activities? Please specify.	
526		Comment: After the section "P.III.B.4.2.1. Pregnancy registries" a section dedicated to studies using pharmacovigilance data would be appreciated. Products with strict risk minimization measures for which very low exposure during pregnancy is anticipated, spontaneous and/or solicited cases that reach pharmacovigilance data sources might be the only option and can provide evidence that is valuable for patients and health care providers. Proposed change: Consider adding a section dedicated to pregnancy surveillance studies.	

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)*
527-541		Comment: Be careful not to restrict to neurodevelopmental outcomes e.g. diethylstilboestrol example. Proposed change: Only refer to neurodevelopmental outcomes as examples of long-term outcomes.	
543, 560		Comment: The information provided is relevant for all pregnancy studies and not only for the studies classified as PASS. PASS is a classification: a study can be classified as a PASS or not. Proposed change: To replace "PASS" by "study" in line 543 and by "studies" in line 560.	
568		Comment: consider adding maternal outcomes (e.g., preeclampsia)	
570		Comment: consider adding a brief explanation for "co-exposure effects".	
616-665		Comment: Risk minimisation should include intensified efforts to ensure appropriate prescribing in women of childbearing age, according to clinical guidelines of the country, to avoid unnecessary exposure. Proposed change: Add "Risk minimisation should include intensified educational efforts to ensure appropriate prescribing in women of childbearing age, according to clinical guidelines of the country, to avoid unnecessary exposure."	
764		Malformation rate: clarify denominator and data source	
770		Comment: Table PIII.2. Clarify how to fill in the table if exposure of a single case occurs across multiple time periods. Moreover, what is the definition of "congenital anomaly" being used here in relation to the terminology as defined in these	

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)*
		guidelines? Suggest indicating factors that impact the timing of "before conception" (e.g., depends on drug half-life, etc)	
820		Comment: typo. "Sexual" should be "sexually"	
821		Comment: "other" (others) should be plural. Consider placing it at the end of the sentence.	
855		Comment: Consider adding exposure window; e.g., "from one year before LMP to the LMP"	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
La Leche League Italia ODV

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement *and* *https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The risk evaluation of drug exposure via breast milk on a breastfed infant or child should take into account the fact that the interruption or cessation of breastfeeding is in itself a risk for the infant's and child's health. So when evaluating risks related to drug exposure, these should be weighed against the risks posed by breastfeeding interruption or cessation. Breastfeeding mothers that must undergo treatments that are not compatible with breastfeeding should receive thorough information on the possibility to maintain lactation through the therapy period and resume breastfeeding afterwards, and about the risks of sudden breastfeeding interruption for their own health (engorgement and mastitis) so that they can make an informed decision about whether to stop breastfeeding or just suspend it. Breastfeeding mothers that must undertake urgent treatments that are not compatible with breastfeeding should also be informed about engorgement management and mastitis prevention techniques. Adverse effects related to engorgement and mastitis could be overlapping with drug effects. When evaluating the risk of an infant or a child to drug exposure via breast milk, important factors to take	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	into account are: the age of the infant or child; whether the infant is in the exclusive breastfeeding period or beyond (these two influence the relative dose received via breast milk); whether the infant is exclusively breastfed or partially breastfed (this may influence both the relative dose and the intensity of adverse effects as an infant receiving formula may be experiencing also adverse effects of the formula itself); for infants and children beyond 6 months of age, the frequency of feeding may vary depending on age, other foods in the diet, and personal choices of the mother. Due to the co-variability of all these factors, the effective risk of drug exposure via breast milk will be increasingly variable among the population with the increase of the child's age, and it will have to be estimated on a case-by-case basis.	

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)*
Lines 59-61		Comment: as breastfeeding is the biological norm, it is inappropriate to speak in terms of "benefits of breastfeeding"; the risks of breastfeeding interruption should rather be considered Proposed change (if any): In the case of breastfeeding, *the risks associated with an interruption of breastfeeding* ~~the benefits of breastfeeding~~ need to be weighed against the risks to the infant from medicine exposure through breast milk, and any effects of medicine use on breast milk production also need to be considered	
Lines 182-188		Comment: in discussing the risk factors for the breastfed child, please consider those that we mention in the general comment and phrase them adequately within this paragraph. Proposed change (if any):	
Lines 423-425		Comment: in its present formulation, this sentence seems to imply that no risk occurs to the child by the cessation of breastfeeding, which is not true as even temporary breastfeeding interruptions pose a risk on a child's health	

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)*
		Proposed change (if any): In situations where a medicine is harmful to the child but use for the mother is imperative, *by weighing the risks of drug exposure against the risks of breastfeeding interruption it is possible to avoid harm to the child during breastfeeding.*~~it is relatively uncomplicated to avoid harm to the child during breastfeeding~~	
Lines 517-520		Comment: in recording possible adverse effects on breastfed children, it is appropriate to distinguish between exclusively breastfed infants and partially breastfed infants, as in the latter case adverse effects of formula may be sum up with adverse effects of the drug. Proposed change (if any): In such cases and if the active substance is present in breastmilk, it is considered useful to additionally include information regarding breastfed infants. The healthcare professionals who fill data in the registry should be encouraged to record whether the mother starts to breastfeed and if so, to ask the mother regarding possible adverse reactions in her infant at each visit; *information on breastfeeding should include whether the infant is exclusively breastfed, partially breastfed, or not breastfed, as adverse effects of the medicine may sum up with adverse effects of formula.*	
Lines 579-582		Comment: Rationale as of general comments	

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)*
		Proposed change (if any): Medicine concentration levels in breast milk samples should be measured and a relative infant dose calculated, to obtain information for supporting the risk assessment and provision of advice on timing of medicine intake relative to breastfeeding where this may be feasible (e.g. for short-term or single dose treatments), *also considering the age of the child and the frequency of breastfeeding*.	
Lines 588-590		Comment: the paragraph on long-term observation of new-born including breastfeeding information should be rephrased to include a distinction between exclusively breastfed children, partially breastfed children and not breastfed children. Proposed change (if any):	
Line 626-629		Comment: interruption of breastfeeding has to be considered a risk to a child's health and maternal health, too, so also these issues should be the object of informed choices by the mother. Proposed change (if any): …enabling women and healthcare professionals to take informed therapeutic decisions for preventing negative impact of maternal use of medicines on the child, preventing unnecessary pregnancy terminations, *preventing unnecessary breastfeeding interruptions,*	

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)*
		promoting adherence to RMM and supporting informed choices where the wish for a child exists	
Lines 657-658		Comment: as breastfeeding is the biological norm, it is inappropriate to speak in terms of benefits of breastfeeding; the risks of breastfeeding interruption should rather be considered. Proposed change (if any): Presentation of potential risks *for the breastfed child in the light of risks deriving from breastfeeding interruption in case breastfeeding is not contraindicated*~~of breastfeeding for the child in the light of benefits of breastfeeding itself if breastfeeding is not contraindicated~~	
Lines from 683 onward		Comment: additional information on breastfeeding suspension should be provided to the mother Proposed change (if any): when treatment reveals as not being compatible with breastfeeding, the mother should receive information about the possibility of maintaining lactation until end of treatment so that breastfeeding can be resumed afterwards.	
After line 758		Comment: It may be appropriate to add information (maybe an appendix of its own) about how to temporarily suspend breastfeeding and maintain lactation, and on how to avoid engorgement and prevent mastitis if the mother has to stop breastfeeding abruptly	

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)*
		Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Netherlands Pharmacovigilance Centre Lareb

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Although this GVP guideline deals with pregnant and breastfeeding women, some remarks about paternal exposure are welcome. This is partially addressed in line 117, but may be elaborated. Combining the text on paternal exposures in a separate paragraph might be useful	
	Put more emphasis in the document on: Importance of knowing the exact timing of exposure in studies, as uncertainties due to estimates or assumptions on intake and the timing might dilute the power Background incidence of outcomes should be ideally addressed within the study itself, as these might fluctuate dependent on the study method Accuracy of essential co-variables / confounding factors is dependent on method of data collection Ideally be able to distinguish missing data from information that can be assured is not applicable	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	(in e.g. Heading P.III.A.1.3, lines 487 -491, Heading P.III.B.4.2.3)	
	In the GVP there is a focus on activities of a specific medical product. However, as a pregnant or breastfeeding women it is also of interest to be able to compare the potential teratogenic effects between medicinal products used to treat the same disease, so instead of a drug specific focus, I think it also should be encouraged to have a disease specific focus in for example PASS studies. In line 487 it is mentioned that epidemiological studies should preferably be carried out using existing data sources and preferably designed in such a way as to minimise bias and confounding. Although we agree with this, we also think it is important to mention that there is a lack of high quality data in this field, and that there is also room for primary data collection to get the data needed.	
	In the section on pregnancy registries more emphasis may be needed to try to avoid medicinal product specific registries and use other options.	

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)*
69		Comment: it is becoming increasingly feasible to access data and generate knowledge on safety in this population. Proposed change (if any):Please address the quality and completeness of these data	
140		Comment: Clinically, gestational age is usually calculated from the last menstrual period, but more accurately 140 established from ultrasound diagnostics Proposed change (if any): true indeed, but out of the scope of this paragraph	
141		Comment: Possible negative consequences of exposure include early pregnancy loss, births defects (teratogenicity), foetotoxic effects, adverse events on the neonate and delayed adverse events on the developing child Proposed change (if any): Add late pregnancy loss	
158		Comment: interference through exposure to environmental agents, including medicines, may result in pregnancy loss or stillbirth Proposed change (if any): true of course, but I assume that the mechanisms involved are described in the previous paragraphs	

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)*
178		Comment: It also means 'birth defects' in general should not be studied as one single outcome Proposed change (if any): Needs additional clarification	
186		Comment: The risk to the child can be different depending on whether the mother takes a single dose or a few doses, or is under chronic treatment with the medicine, and whether she took the medicine already during pregnancy or initiated treatment during breastfeeding. Proposed change (if any): Add age child	
194		Comment: Terms for defining the foetus at the different stages of the pregnancy are: Proposed change (if any): Add definitions of, at least, the first trimester	
212		Comment: late foetal death (after 22 completed 212 weeks of gestation) is known as stillbirth. Proposed change (if any): Add stillbirth to the list of terms	
214		Comment: ***Miscarriage***: Spontaneous abortion and molar pregnancy. Proposed change (if any): Make 'molar pregnancy' a separate entity	

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)*
224		Comment: ***Birth weight***: Initial weight of the infant at birth. Proposed change (if any):Add in grams	
235		Comment: If it is *usually* below the tenth percentile, it is advisable to either provide a proper definition of IUGR or give the percentile value. The current description is not specific. Proposed change (if any): amend current text	
258		Comment: ***Teratogen***: A medicine or other environmental factor that can cause congenital abnormalities. Proposed change (if any):Traditional abnormality or more up to data anomaly?	
259-260		Comment: The definition in major anomaly, but in the text your write the prevalence of major abnormalities is 2-4%. Proposed change (if any): Do you really mean abnormality here or maybe you mean anomaly?	
259-260		Comment: likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment. Proposed change (if any):Add cosmetic relevance	
261		Comment: in line 169 it was stated that around 3% had a birth defect.	

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)*
		Proposed change (if any): Describe more uniformly	
270-274		Comment: since the multiplication has an impact on the unit of the prevalence rate (per 1000 or per 10,000) provide the correct unit as well.	
274		Comment: ***Total prevalence rate=*** Number of live births, stillbirths and terminated pregnancies Proposed change (if any):All terminated pregnancies irrespective knowing if there was a MA yes or no?	
275		Comment: Proposed change (if any):Add terms for maternal and neonatal death	
285		Comment: I assume GVP V will be adopted accordingly?	
317		Comment: and/or the suspected medical product was taken by the father Proposed change (if any): In the ICH-e2b-R3 format Route of administration there is no option to indicate that the father might be the source of the drug exposure of the embryo/foetus (for maternal transmission this is available in the trans placental and trans mammary options).	
317-318		Comment: Should be followed-up in order to collect information of the outcome of the pregnancy and the	

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)*
		development of the child after birth. It is not clear for how long follow up should be obtain, as developmental changes can occur with a late onset. Proposed change (if any):	
335		Comment: at Lareb, we use the MedDRA term "Maternal exposure during pregnancy" in the reaction/event section, according to the MedDRA Term Selection: Points to Consider, instead of 'Exposure in utero'.	
349		Comment: As many specific data elements as are possible to be obtained should be included Proposed change (if any): Seems logic, wouldn't it be better to also include minimal requirements	
365		Comment: provided in months, weeks, days or trimester Proposed change (if any): Remove trimester, this is not specific enough	
379		In table P III.1 and in footnote 7, it is mentioned no ICSR is required when there is no adverse reaction in mother and no adverse reaction in child. However, the absence of adverse reactions in pregnancy or lactation is very valuable information. We (Netherlands Pharmacovigilance Centre Lareb) receive this type of report occasionally and have not rejected or nullified these so far. We code the Reaction using MedDRA LLT's "Normal pregnancy" and	

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)*
		"Normal newborn". Please clarify whether this course of action is allowed, even though it is not a requirement.	
510		Comment: Registries should be inclusive rather than exclusive by means of comprehensive inclusion criteria. Proposed change (if any): please explain what is meant	
579		Comment: Medicine concentration levels in breast milk samples should be measured and a relative infant dose calculated, Proposed change (if any): Add bases on AUC (not only single measurements)	
594		Comment: A more detailed approach for detecting potential safety signals in spontaneous reports is missing. Given the focus on data collection, a separate paragraph on the detection of safety signals is advisable. Proposed change (if any):	
666		Comment: Risk minimisation may not be limited to avoiding exposure in utero and during breastfeeding. Well considered risk minimisation may result in continuing use of the medication by the mother, when the risk of discontinuation or switching outweighs the (limited) risk of continuation. For instance: Poor treatment of chronic maternal disease may result in increased risk of IUGR or preterm birth. And the benefits of breastfeeding outweigh the risks of the exposure of the infant (if any) for most drugs.	

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)*
800-802		Comment: Further specification might be of value; knowing the method of data collection (medical records, interview, online questionnaire etc) Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
[redacted] (ENTIS, UKZN)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Content: 1. This guidance refers to and includes content from prior guidance with the instruction that the earlier guidance is consulted, suggesting that the intention is not for this new GVP guidelines to replace earlier guidance. The content of the older guidelines is however not fully aligned and needs review alongside the GVP III pregnancy and breastfeeding guidance. This relates in particular to: a) CHMP/203927/2005 CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation from Data to Labelling b) CHMP/313666/2005 CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post authorisation Data (EMEA/CHMP/313666/2005), drafted 2005 nd published 2008. CHMP/203927/2005 - focuses heavily on malformations.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	- Needs to be updated to include reference to adverse effects other than malformations (neurodev etc) - Guidance for risk assessment and recommendation for use of a product in lactation would be useful (possibly similar to Appendix 1 for pregnancy) Suggestion: Review and stakeholder consultation of the old guidance please 2. There are a number of areas in the introductory section of this new guidance where the wording is ambiguous or terminology possibly not correctly defined. Review and insertion of references to the source published text would strengthen the content is suggested. 3. The addition of pragmatic, evidence based and expert reviewed guidance on contraception and pregnancy testing in the context of the PPP is extremely helpful. 4. Whist this guidance offers the added benefit of having legislative guidance relating to pregnant and breastfeeding women collated from multiple other GVP modules into one document, it lacks the provision of much	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	needed added detail to improve the application and implementation of existing guidance. For example, it would have been very helpful for this new guidance to have covered : a) Implications of the ENCePP Code of Conduct in the practical application of GPV guidance b) guidance as to the minimum length of follow-up for pregnancy registries or pregnancy case reports c) clarification as to which long term outcomes need to be monitored for d) guidance on the neurodevelopmental outcomes that need to be assessed e.g composite measures such as IQ versus measurement of component functions such as language, motor development etc versus outcomes such as ADHD, autism e) the recommended assessment tools / questionnaires for neurodevelopmental assessment f) guidance on longer term follow-up of already reported / recruited exposed pregnancies in a pregnancy registry or active / enhanced surveillance program that is closed on the basis that the number of first trimester exposures stipulated in existing guidance	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	provide no evidence of increased risk for congenital malformations. g) Development of P.III. Appendix 1. Questionnaire to collect information on pregnancy exposure (unchanged since 2005 guidance) from a high level list of categories to a more structured list of data fields for which a standardised coding system or unit of measurement is provided where appropriate h) An approach to analysing pregnancy or breastfeeding exposure surveillance data 5. It would be useful to include a section summarising what changes / improvements this guidance adds to existing guidance in terms of practical implementation of the legislation 6. The only reference in the guideline to the need for multidisciplinary expertise is under the heading of long term outcomes. Analysis of any pregnancy exposure data requires a high level of expert involvement. It is important to recognise that those who do not have experience in this area cannot rely solely on theoretical guidance.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	7. Cross-reference of (and ideally alignment between) EMA and FDA pregnancy and breastfeeding focused guidelines would be extremely helpful and beneficial **<u>Structure:</u>** I did not feel that P.III.A and P.III.B combined / flowed together well. It was like reading two completely separate documents, both in terms of writing style and content. The content of this new GVP also seems very mixed. It includes very brief methodological guidance for analysing and interpreting the data, some background theory, legislative instructions identified within large passages of text by 'should' as well as operational instructions as to how to complete the reporting documents. Personally, I think that P.III.A and P.III.B should be separated into separate documents possibly as follows: 1. The newly added detail in P.III.A is integrated into the existing CHMP/313666 document as a revision of this guidance. As it is, large sections from CHMP/313666 are carried over	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	to the new GVP guidance. Most of 313666 remains valid and provides an essential background / introduction to PV in pregnant and breastfeeding women. CHMP/313666 is clearly written and structured. I did not find the new GVP guidelines as easy to read and follow. Many of the sentences are very long and complicated. I preferred the flow and structure of CHMP/313666/2005. 2. P.III.B to form the basis of the new GVP III for pregnant and breastfeeding women, pulling together, expanding on and contextualising all relevant information, legislation and guidance for pregnant and breastfeeding women from the other GVPs. Simultaneously, CHMP/203927/2005 CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation from Data to Labelling to please be updated and aligned.	

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)*
69		Comment: Methodological studies are needed to assess the suitability of existing data sources for pregnancy PV Proposed change (if any): Include reference to above	
71		Comment: Findings need to be fed back into the SmPC in a timely manner for this to happen. Just as important for normal outcomes to be recorded. Proposed change (if any): To be considered within the guidance	
81 - 85		Comment: This paragraph seems out of place and beaks the flow of preceding and following information, clarifying that the guidance provides no new regulations but serves to collate the specific pregnancy and breastfeeding guidance in other GVP modules Proposed change (if any): For readability suggest move paragraph 81-85 to before text commencing line 101 or after 103	
106		Comment: The title of this section does not fit with the content	

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)*
		Proposed change (if any): Change title e.g. to 'Factors predictive of teratogenic risk…'	
126		Comment: and to changes in the unbound or free/ active fraction Proposed change (if any): add	
128		Comment:'….impact on maternal health or directly on the pregnancy' Proposed change (if any): insert underlined text	
134		Comment: Consequently, where possible, collection of such PK data during PASS or controlled trials is important. The FDA have recently issued guidance on the inclusion of pregnant women in RCTS Proposed change (if any): add sentence , reference FDA guidance	
141		Comment: Pregnancy loss can be early or late Proposed change (if any): change wording to 'pregnancy loss'	
143		Comment: (incorrect grammar + content) – risk of adverse effects extends beyond childhood. Given recent	

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)*
		experience with valproate, specific reference to neurodevelopmental impairment is warranted here Proposed change (if any): Edit as follows: ` adverse events in the neonate and delayed adverse events in the developing child, during adult life or even transgenerationally. Of particular concern is the risk of neurodevelopmental impairment following *in utero* exposure, often only clinically detectable in later childhood,	
147		Comment: while the period of malformation risk is not incorrect given the long period of fetal brain development, weeks 4 to 10 of pregnancy, or less specifically the first trimester, is considered the main period of susceptibility for structural malformations Proposed change (if any): insert diagram showing timing of fetal organ development and susceptibility	
148		Comment: 'significant birth defects or neurodevelopmental impairment' Proposed change (if any): add underlined text	
161-162		Comment: This is not correct.	

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)*
		The concept of competing endpoints refers to viability, not birth defects directly ie. A pregnancy can only end in ETOP or SA or LB or SB. However, any of these outcomes could involve a birth defect. Proposed change (if any): add text as underlined ' evaluating the frequency of brth defect in livebirths…'	
162-165		Comment: This is not quite correct Proposed change (if any): A product that does not cause structural malformations may still perturb brain development. Where a teratogenic syndrome is recognised on the basis of dysmorphic features or a structural malformation syndrome, the risk of associated neurodevelopmental effects is likely to be increased.	
169		Comment: ? reference for this, generally a rate of MAJOR birth defects is quoted at around 2-3% Proposed change (if any): check and reference source	
178		Comment: Does not align with co-existing guidance that states that overall rates of CM need to be analysed given rarity of individual CMs	

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)*
		Proposed change (if any): Need to align guidance documents	
193		Comment: I think that these should remain an annex / appendix as they were in CHMP/313666/2005 Proposed change (if any): Move to appendix	
193		Comment: Trimesters not defined Proposed change (if any): Add definition of trimesters	
232,237 and 239		Comment: 3 new definitions added to CHMP/313666/2005 Annex 4. Unable to find these in the ICD10 Proposed change (if any): check from ICD10 or reference alternative source accordingly.	
286		Comment: if data are available regarding fetal risk following exposure in pregnancy or breastfeeding for products where use is <u>not</u> anticipated in women of child bearing potential this should still be reflected in the summary of safety specifications Proposed change (if any): consider above proposed change	

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)*
324		Comment: P.III. Appendix 1. Questionnaire to collect information on pregnancy exposure is unchanged since 2005 guidance 15 years ago. Given that these revised GVP modules aim to improve the implementation of the legislation and to improve PV practice, modification of the current ICH-E2B template to capture the required fields in a structured and systematic manner needs to be considered as a matter of priority. Suggesting that the information be provided in the narrative is suboptimal, both in terms of optimising the completeness and accuracy of data collection, as well as the readiness of data for automated signal detection. Proposed change (if any): Addition of specific structured data fields/ elements to the existing ICH-E2B forms for pregnancy PV	
333-339		Comment: No guidance on how to code paternal exposure included. Was previously provided in CHMP/313666/2005 Proposed change (if any): Guidance to please be reviewed and provided	
356		Comment: The current definition of a 'prospective' report introduces an inclusion bias that could prevent the recording of teratogenic effects in the resulting 'gold	

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)*
		standard prospective cohort' which by virtue of this definition will only include pregnancies that have had a normal prenatal scan.....!!. The presence or absence of an abnormal prenatal test should not be the determining factor for a report being prospective or retrospective, but rather whether or not a prenatal test has been done at the time of reporting. Where is the origin of this definition? If from another guideline, how was this definition agreed? Historical (and still in use) definitions of prospective versus retrospective depended on whether the birth outcome was known or unknown at the time of reporting, NOT whether it was normal or abnormal Proposed change: The definition of / criteria for prospective versus retrospective needs to be reviewed.	
365		Comment: Gestational age at the time of exposure to a medicinal product during pregnancy is one of the most important factors in assessing teratogenic risk. To improve the quality of data that is collected reporters should be asked to report the exposure window as accurately as possible. The current draft document allows for greater uncertainty / vagueness in reporting than existing guidance. Instead reporters should be trained to provide accurate information.	

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)*
		Proposed change: Replace current text of 'months, days, weeks or trimester" with a request that the day or week of pregnancy is reported, and ONLY where this is not possible the month or trimester is used, and the temporal relationship between the observed adverse reaction and exposure is described.	
379		Comment: The table for requirements for the submission of ICSR with pregnancy exposure is unchanged from CHMP/313666/2005. It does not seem logical or conducive to accurate data analysis that an AR in mother + SA Or Foetal death without CM is classed only as 1 case <mother>, with the same being true if there is No AR in the mother. This seems to be very CM centric. Reassessment of prior guidance needs to be part of this update Proposed change (if any): Review existing guidance that has been pulled through to, or cross referenced in, this document	
444		Comment: What is long enough or who decides when the follow –up period is sufficient? Proposed change (if any): Practical guidance is needed as to the required period of follow-up.	

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)*
454		Comment: Dose adjustments are not informed by changes in plasma levels alone. Correlation with clinical features of the disease is key. Some conditions improve during pregnancy. Even if the serum concentration fell, a dose increase may not be indicated in this place and potentially puts both fetus and mother at unnecessary increased risk. Oversimplification of this section carries the risk of the non-expert misinterpreting the background information. Proposed change: Include reference in the text to the importance of the correlation of clinical findings to drug levels (not many studies provide this). It is not as simple as treating the laboratory result.	
471		Comment: Is this a previously validated / published definition of a Medicines safety study? It doesn't seem clear to me. Proposed change (if any): Please check wording and reference the source of the definition	
516		Comment: Ambiguous wording Proposed change (if any): Reword ` ….evaluation of development beyond the neonatal period or infancy.	

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)*
540		Comment: also need expertise in teratology and pregnancy statistics Proposed change (if any): add 'teratologist, statistician with expertise in pregnancy exposure studies' to list	
770		Comment: Table for submission of PSUR unchanged from CHMP/313666/2005. Critical review of required reporting format is warranted .e.g. No capture of cases Lost To Follow Up is requested, no request for information on neurodevelopment or other long term outcomes. There is also opportunity here to perhaps ask the reporter, if applicable, for summary statistics of their dataset to capture how many pregnancy reports they have for the exposure in question, how many normal, abnormal etc Proposed change (if any): Review existing guidance that has been pulled through to this document.	
786		Comment: Given that the questionnaire has remained unchanged for 15 years, it is surprising that n Proposed change (if any):	
		Comment:	

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)*
		Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
MEB

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Long-winded and sort of a textbook instead of a guideline. There should be more reference to appropriate GVP modules, to avoid repetition of information in these 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)*
Lines 48-52		Comment: should the chapter be renamed as: women of childbearing potential (WOCP), pregnant and lactating women? What is the scope of this guideline? Proposed change (if any):	
Lines53-55		Comment: this sentence should be moved to the end of the paragraph, mentioning first the exception is confusing. Proposed change (if any):	
Lines 77-80		Comment: this paragraph is in contract with the first paragraph. Proposed change (if any):	
Line 83		Comment: please add the following Proposed change: …….. refers to the result of a pregnancy **with positive or negative outcome** and hence may ……	
Lines 88-89		Comment: this sentence is in contrast to the first paragraph of the document.	

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)*
Line 118		Comment: there are studies on exposure through semen, therefore 'unkown' should be replaced by 'hardly known'.	
Lines 193-275		Comment: too detailed and to elaborate. Is this discussed with experts of for instance EUROCAT and ENTIS?	
Lines 296-299		Comment: It is only mentioned that this should be in the RMP, but it is crucial to have this information in the product information.	
Line 308		Comment: 'potential risk' is stated, but it is not clear whether "important potential risk" is meant and as such included in the list of safety concerns of the RMP.	
Lines 326-376		Comment: this is sort of redundant by referring to the appropriate GVPs VI and annex IV in which this is discussed. Otherwise there is a lot of overlap. Provide only requirements specific for pregnancy and lactation cases.	
Line 417		Comment: 'Drug utilisation study' is stated here, but this should be replaced by 'study with appropriate design', because a DUS is hardly performed in investigations regarding pregnancy. There are more appropriate designs to investigate pregnancy outcomes that are more state-of-the-art.	
Line 453		Comment: 'sometimes' is mentioned for studying free plasma levels, this should be explained by the fact that free plasma levels are important in case of high protein binding of the medicine.	
Line 461		Comment: In this section it should be referred to the "CHMP guideline on the exposure to medicinal products during	

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)*
		pregnancy: need for post-authorisation data" in which all sorts of epidemiological studies designs are described.	
Line 465		Comment: Again the list is started with drug utilisation studies, however for investigating pregnancy outcome this is not the most appropriate study design. At least the list should start with 'case-control studies'.	
Lines 485-486		Comment: this last sentence should be deleted as is not applicable.	
Line 542		Comment: this section should refer to GVP module VIII PASS in which handling of bias and confounding might be discussed.	
Lines 543-570		Comment: based on the remark above, this section should focus specifically on needs of this specific population.	
Line 594		Comment: It should be considered to add also cases of pregnancy and lactation to the eRMRs in line with the other special populations paediatric cases and cases of elderly.	
Lines 640-665		Comment: This is too detailed and might be mentioned in GVP module XV, to avoid repetition	
Lines 695-758		Comment: this is part of GVP modules V and XVI. Specific measures should only be stipulated here, so these lines can be deleted. Change: Line 695 etc. should list: - educational material - PPP - advice on effect contraception	

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)*
		Followed by reference to the appropriate GVP	
Lines 887-922		Comment: this appendix is redundant, because pregnancy testing prior to teratogen prescription should be clearly described in the concerned educational materials and product information. Furthermore, the table with reliable contraceptive methods is not complete and is liable to new methods and treatment options for updating.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Medicines for Europe Rue d'Arlon 50 1000 Brussels Belgium Contact person: [redacted]

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	From the introduction and terminology part is seems that the guideline is applicable from the conception and not before, while we would advise it also addresses the risk of teratogenicity or mutagenicity and impact on gamete. There are already some additional risk minimisation measures in place in the EU (eg. retinoids, mycophenolate) which require additional wash out period, and propose precaution and timelines to be considered before pregnancy, or have also warnings for the father. Later parts of this guideline related to epidemiology and risk communication give opportunity to explore or communicate risk during preconception period. To ensure consistency, it is advised that introduction P.III.A would also address further preconception period for both mother and father for the teratogenic risk. It is advised P.III.A would cover also drug exposure through semen, similarly as addressed in P.III.A.1.1.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	P.III. Appendix 1, section C on paternal exposure has no details regarding "Medical products exposure" as compared to maternal exposure. We would advise the following would be added: dosage, date of first use, date of end of treatment and duration.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	This is basically a comment to E2B R3, to add data elements for structured fields such as 'prospective' or 'retrospective' to allow easier analysis for the regulators and MAHs. The MAH may not always have access to the narrative (e.g. EV cases) while follow up may be needed which may end up in follow up of a specific case by a few companies on data that was already initially provided by the reporter which will burden the system.	

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)*
145-154		Comment: Proposed change (if any): Suggest to separate gestational weeks from different periods. E.g.: Gestational week 0-3; Gestational week 4-15; Gestational week 16 to delivery.	
158-159		Comment: concerning the description of the period "throughout pregnancy", suggest to include birth defects. Insertions in **bold**. Proposed change (if any): Original: Throughout pregnancy: interference through exposure to environmental agents, including medicines, may result in pregnancy loss or stillbirth as well as birth defects.	
160-161		Comment: Suggest to align term birth with live birth as in P.III.A.2. Terminology. Proposed change: "…then only evaluating the frequency of **live** birth defects would underestimate…"	
165-166		Comment: Not all medicine exposure will lead to adverse pregnancy outcomes long after exposure has occurred.	

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)*
		Proposed change: "Some adverse pregnancy outcomes **may** only become apparent long after exposure has occurred, as the child develops, irrespective of when the exposure occurred."	
169		Comment: ..."~3% of all live births..." Proposed change: Please include reference	
170-171		Comment:"... has been reported ..." Proposed change: Please include reference	
188-189		Comment: The medicinal product itself will not be excreted in breast milk. Substances of interest should be the active pharmaceutical ingredient, and metabolites thereof if applicable. Proposed change: "PK data of ~~a product~~ **the active substance and/or its metabolite(s)** in breast milk can help inform the level of exposure from breastfeeding."	
189-192		Comment:	

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)*
		The data that could be made available in a post-marketing setting, may be very difficult to validate and interpret in such settings (e.g. PK data in child depends on quantity ingested which is usually unknown, timing of sampling and drug exposure may have a big impact on the result). Proposed change: "PK data in a child after intake of a medicine with breast milk provides some information about the possible risk to a child, and when an adverse reaction is suspected in a breastfed infant, it may be valuable to obtain a blood sample from the child. **However, it is acknowledged that this is usually not feasible and the data difficult to validate, analyze and interpret in the routine postmarketing environment.**"	
207-208		Comment: Suggestion to align definition of pregnancy outcomes with lines 142-143 where also births defects (teratogenicity), foetotoxic effects and delayed adverse events on the developing child are included. Proposed change: "***Pregnancy outcome:*** End result of pregnancy, which includes ectopic pregnancy, miscarriage, foetal death, termination of pregnancy and live birth**, births defects (teratogenicity), and foetotoxic effects**.	

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)*
250-257		Comment: Suggest to harmonise the definition of congenital abnormality with the definitions of "isolated" congenital abnormality and "multiple" congenital abnormalities. Insertions in **bold**. Deletions with strikethrough. Proposed change (if any): Original: Congenital abnormality (structural birth defect, sometimes congenital malformation, foetal defect): A**n** ~~consequence of~~ error of morphogenesis, i.e. structural-morphological defect, grossly or microscopically present at birth whether detected at birth or not. Isolated congenital abnormality: A single localised error of morphogenesis. Multiple congenital abnormalities: A concurrence of two or more different morphogenetical errors, i.e. component congenital abnormalities in the same person.	
258		Comment: Suggestion to add lifestlye factors to include factors like alcohol. Proposed change: ***Teratogen***: A medicine or other environmental **or lifestyle** factor that can cause congenital abnormalities.	
261		Comment: "…2%-4% in most series published"	

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)*
		Proposed change: Please include reference(s)	
292-295		Comment: Not all types of risk minimisation measures do lead to recognition of safety concerns in the summary of safety specifications. To avoid ambiguities, we would advise it is clarified that this sentence refers to additional risk minimisation measures. Proposed change: "For all three categories of safety concerns, recognition in the summary of safety specifications usually implies that additional pharmacovigilance activities for data collection and/or **additional** risk minimisation measures may be needed (see GVP Modules V and XVI)."	
315-319		Comment: ***P.III.B.2. Management and reporting of adverse reactions*** Proposed change (if any): Original: Reports where the embryo or foetus may have been exposed to (a) medicinal products(s) (either through maternal exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth. Any further specific recommendation in terms of minimum number of follow-up and/or duration?	

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)*
341		Comment: The term "prospective" is introduced here for the first time while the definition of this term is only provided later (lines 353-362). Proposed change: Consider adding a definition of prospective or alternatively move this section after the definition.	
390-391		Comment: Age and sex-specific drug utilisation data are not always available. Proposed change: Age- and sex-specific drug utilisation data need to be included, **if available** (in PSUR section "Estimated exposure and use patterns"),	
402-403		Comment: Based on GVP-Module VII Rev. 1, MAH presents spontaneous reports of adverse pregnancy outcomes in section "Signals and risk evaluation" if Use during pregnancy is recognized as a safety concern for product in question. Otherwise, pregnancy and breastfeeding cases are presented in section 9. "Information from other clinical trials and sources". Proposed change: **For products for which use during pregnancy is a recognized safety concern, the** ~~**O**~~occurrence of spontaneous reports of adverse pregnancy outcomes	

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)*
		should be presented in the PSUR section 'Signal and risk evaluation'. **For products for which use during pregnancy is not a recognized safety concern, occurrence of spontaneous reports of adverse pregnancy outcomes should be presented in the PSUR section 'Information from other clinical trials and sources'.**	
474, 486		Comment: Based on GVP V Rev.2 effectiveness evaluation is mainly measured for additional RMM. Proposed change: 474 "Studies to evaluate the effectiveness and broader impact of **additional** RMM."486 "time with implementation of **additional** RMM in specific populations."	
487-491, 495-497, 499		Comment: MAH agrees with the statement such as preference of secondary database use, preference of use of the disease rather than product registries when possible and including participants from more than one country to collect more data. We would suggest that when product-specific registries do exist, MAH specific registries would be avoided, because additional registries for individual generic MAH are not feasible from scientific point of view. Proposed change: Line 499:	

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)*
		• In exceptional cases, a medicinal product-specific pregnancy registry may be appropriate**, however when a registry already does exist, creation of an additional registry for generics should be avoided due to limited exposure to medicines in such additional registries**;	
495		Comment: Add "disease" registry for clarity Proposed change: "**Disease r**egistries that…"	
761-763		Comment: It is stated that for products with pregnancy or **breastfeeding** related safety concerns Table P.III.2 should be provided. However, below in the Table P.III.2 only pregnancy cases are mentioned. As per GVP Module VII, the focus of the evaluation(s) in sub-section "Evaluation of risks and new information" is on new information which has emerged during the **reporting interval** of the PSUR in the context of cumulative information. Proposed change: For ~~**all teratogenic products and for**~~ those products with pregnancy ~~**or breastfeeding**~~ related safety concerns in the RMP or the PSUR, Table P.III.2. should be provided in the PSUR and filled in completely with reporting period	

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)*
		interval ~~**and cumulative**~~ data. **In case new information emerges from the analysis of interval information, cumulative data should be taken into account. In PSURs of products which have suspected teratogenic/mutagenic potential, or new chemical entities, analysis of cumulative pregnancy data should be performed.**	
761-770		Comment: Content of section P.III.C.1. Submission of period safety update reports in the EU, including table P.III.2.: "Table for reporting numbers of individual case safety reports in periodic safety update reports", is more related to PSUR content so we would suggest this section is removed while its content is moved to section P.III.B.3. Periodic safety update report. Proposed change: Move content of section P.III.C.1. from P.III.C to P.III.B.3. Periodic safety update report (can be added as last bullet after line 408).	
770		Comment: Regarding **table content**, in some cases it is difficult to obtain all relevant data, e.g. outcome of the pregnancy case could be unknown.	

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		Proposed change: Additional row in the Table P.III.2 should be added for pregnancy outcome: Unknown.	
770		Comment: The column heading refer to "Before conception". We suggest to replace with "before last menstrual period" as this data is usually available (and requested in Appendix 1). Proposed change: Before **last menstrual period ~~conception~~**	
770		Comment: The row heading includes "Stillbirth without foetal defects". consider adding "unknown" as it may be unknown whether there were foetal defects. Proposed change: Stillbirth without foetal defects **or unknown**	
770		Comment: The row heading includes "Live birth without congenital anomaly". Consider adding "unknown". Proposed change: Live birth without congenital anomaly **or unknown**	
770		Comment: It is clear that there can be only one marking/count per case to give a correct total number of cases, however it would be good to have guidance on how to mark in the table when there is an overlap of periods (e.g. or example, a woman exposed in 1st and after 1st trimester). Proposed change:	

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)*
		Add clarification how to populate table when timing of exposure is overlapping.	
810-816		Comment: Suggest to add specific information on drug product and vaccine exposure to "obstetrical history". Insertions in **bold**. Proposed change (if any): Original: Obstetrical history - Number of previous pregnancies and outcome (live birth, miscarriage, elective termination with specification of gestational length and context, late foetal death, ectopic pregnancy, molar pregnancy) - Previous maternal pregnancy complications - Previous foetal/neonatal abnormalities and type **-- If Yes, did the abnormality occur following an exposure to medication and/or vaccine?** **-- If Yes, specify the medication and/or vaccine name(s) and period of exposure as in the example below.** **PRODUCT1 NAME – Within [X] month(s) before pregnancy / Gestational week [X] to [Y] / Late pregnancy / During delivery** **PRODUCT2 NAME – Within [X] month(s) before pregnancy / Gestational week [X] to [Y] / Late pregnancy / During delivery** - History of subfertility	
817-822		Comment: Suggest to add history of maternal immunisation and blood product exposure to "maternal medical history". Insertions in **bold**	

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)*
		Proposed change (if any): Maternal medical history Risk factors for adverse pregnancy outcomes including environmental, occupational, substance abuse exposures and medical disorders such as hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS (specify viral load, CD4 count), and other, including other predisposing factors for neurodevelopmental disorders. **Maternal immunization history (i.e. previous immunizations and any adverse event following immunization (AEFI)).** **History of exposure to blood products (e.g. blood transfusions).**	
823-842		Comment: Suggest to add "Exposure to vaccines" to the "Current pregnancy" section. Insertions in **bold**. Proposed change (if any): Original: [...] - Exposure to products subject to medical prescription, OTC products, pregnancy supplements such as folic acid, multivitamins: ⇒ Name ⇒ Dosage & route ⇒ Date of first use, date of end of treatment, duration ⇒ Indication **- Exposure to vaccines:** **⇒ Name** **⇒ Route of administration**	

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)*
		⇒ Date of first dose **⇒ If additional doses were administered, specify dates** [...]	
902		Comment: Lines 908-909 state that Less effective methods are based on greater than 1% failure rate, while table (line 902) states these as effective methods. Proposal to align table with text as highly and less effective methods are both effective methods. Proposed change: Add "less" in table in line 902 to say "**Less ~~E~~e**ffective methods".	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
[redacted], Midwife – National Institute of Health, Rome
[redacted] Midwife – National Institute of Health, Rome

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Thank HMA for having a document addressing pharmacovigilance during pregnancy and breastfeeding. Basing on my previous experience of research on pharmacovigilance during breastfeeding, I am giving some suggestions for the HMA document. - In some parts of the document, while the pregnancy topic is well developed, the breastfeeding is missing or unclear (e.g. P.III.B.5 Signal management, P.III.B.6. Safety Communication). - Despite being out of the scope of this document, the MedDRA system contains some codes that should be changed, using a more appropriate language, i.e. "Intoxication by breast feeding" should be "Intoxication through breast feeding", as the intoxication is due to external exposure (e.g. chemicals), not by breastfeeding itself. There are some other concepts included in the MedDRA system that should be reviewed. - The MedDRA system include the "Bottle feeding" code. In fact, there are a number of suspect ADRs due not to "the bottle" in itself, but due to infant and follow on formulas. In Europe, prebiotics, probiotics or other fortifiers are added to infant	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	formulas with no supporting evidence or a structured post marketing surveillance system. EFSA and HMA should consider to address this topic, as mothers are reporting to clinicians a number of suspect ADRs due to formula. Probably these are not ADRs, but we will never know unless we provide a structured reporting system including Breast Milk Substitutes.	

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)*
46-47		Comment: "Pregnant and breastfeeding women are considered vulnerable, or special populations," Pregnant and breastfeeding women are healthy persons and, due to biological changes, can be considered special populations. I suggest avoiding the term "vulnerable". Proposed change (if any): "Due to the specific biological condition, pregnant and breastfeeding women are considered special populations,"	
52		Comment: I suggest to add the following sentence, based on available evidence on women's attitudes. [1] Proposed change (if any): "Furthermore, some women perceive as a potential risk the use of medication during breastfeeding. This attitude may lead to discontinue breastfeeding, discontinue the medical treatment or to self-treat using "natural products", that are perceived as safer for the baby.	
61		Comment: I suggest to change "breast milk production" with "lactogenesis" (including lactation stages I, II and III)	

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)*
		Proposed change (if any): change "medicine use on breast milk production also need to be considered" To "medicine use on lactogenesis also need to be considered"	
362		Comment: In order to estimate the infant exposure to medications, it is important to assess the breastmilk intake. In the report, I suggest to use the WHO definition and questions, with a 24 hrs recall period. Despite having being thought for monitoring purposes, they apply also to clinical use. Proposed change (if any): As for retrospective and prospective data on breastfeeding, in order to estimate the infant exposure to the medications through breastmilk it is necessary to collect data as type of feeding and the approximate number of breastmilk feeds/24 hours. It is suggested to collect data on the type of feeding using the World Health Organization definitions (exclusive or predominant breastfeeding, complementary feeding) and the standard questions below, with a recall period of 24 hours: 1. In the last 24 hours the baby had: - Breastmilk Y/N - Formula or animal milk Y/N	

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		- Other liquids (water, herbal teas, juices) Y/N - Other foods (porridge, soup, biscuits, yogurt, …) Y/N A supplementary question is: 2. If the baby is not exclusively breastfed, how many breastmilk feeds per day?	
576-577		Comment: This suggestion derives from analysis of 21.700 records of breastfeeding women that have called the Toxycology Information Centre in 2015 (data not yet published) Proposed change (if any): Change "(e.g. antidepressants, anti infectives, diabetes medications, pain medications)" To (e.g. antidepressants, anti infectives, diabetes medications, pain medications, and medicines used in other chronic conditions as hypertension, cardiovascular diseases, epilepsy, multiple sclerosis)	
587-588		Comment: The milk sampling method for lactation studies derives from FDA "Clinical Lactation Studies: considerations for study design. Guidance for Industry. Draft Guidance." May 2019 [2]	

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)*
		Proposed change (if any): Change "This may include the clinical follow-up of breastfed children whose mothers are treated with a specific medicine." To "This may include the clinical follow-up of breastfed children whose mothers are treated with a specific medicine or studies based on breastmilk sampling in mothers that have temporarily or permanently discontinued breastfeeding.	
588		Comment: Proposed change (if any): Change "new-borns" To "newborns"	
595		Comment: it is unclear if this part refers also to breastfeeding. In this case, I suggest the following Proposed change (if any): Change "Signal management activities of adverse pregnancy outcomes"	

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)*
		To "Signal management activities of adverse pregnancy/breastfeeding outcomes"	
608		Comment: I suggest adding information on Standardised MedDRA Query (SMQ) to design an appropriate search strategy addressing breastfeeding. Proposed change (if any): I suggest to add "The same Standardised MedDRA Query (SMQ) (1st level) 602 'Pregnancy and neonatal topics' can be used to retrieve 'Lactation related topics (incl neonatal exposure through breast milk)' (SMQ), that include 'Functional lactation disorders' and 'Neonatal exposures via breast milk'.	
624-629		Comment: See papers [1,3,4] Proposed change (if any): Add to: "The specific communication objectives discussed for medicines which may be used by women who are of child-bearing potential, planning a pregnancy, or are pregnant or breastfeeding, relate to enabling women and healthcare professionals to take informed therapeutic decisions for preventing negative impact of maternal use	

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)*
		of medicines on the child, preventing unnecessary pregnancy terminations, promoting adherence to RMM and supporting, informed choices where the wish for a child exists." The following: "As for lactating women, appropriate safety communication would result in preventing unnecessary temporary or permanent interruption of the mother's medical treatment or breastfeeding disruption."	
640		Comment: Effective safety communication can be promoted through appropriate labelling [3] and e-learning program, that have been proved to be effective on the specific "use of medications during breastfeeding" topic [5,6] Proposed change (if any): Add a short paragraph on the use of labelling and on e-learning as a mean to promote effective safety communication.	
657-660		Comment: Proposed change (if any):	

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)*
		Change: "Presentation of potential risks of breastfeeding for the child in the light of benefits of breastfeeding itself if breastfeeding is not contraindicated, and advice on dose-reduction, timing of breastfeeding in relation to medicine intake, monitoring and early detection of adverse reactions on the child and when to seek medical advice;" To "Presentation of potential risks of breastfeeding for the child in the light of benefits of breastfeeding itself if breastfeeding is not contraindicated, and advice on dose-reduction, timing of breastfeeding in relation to medicine intake, monitoring and early detection of adverse reactions on the child and when to seek medical advice, temporarily interruption of breastfeeding, resuming of breastfeeding and relactation;"	
683		Comment: See the proposed "Medications and Breastfeeding Algorithm", page 331 [1] Proposed change (if any):	
714-721		Comment: see the above comments (line 640) to suggest dissemination of educational materials to health professionals through e-learning systems (cost-effective),	

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)*
		and to provide appropriate medication labelling on breastfeeding	
856-877		Comment: consider adding questions on feeding type and practices, using the WHO questions, as suggested above (line 362)	

Please add more rows if needed.

[1] Colaceci, S., Giusti, A.,… & Alvaro, R. (2016). Medications, "natural" Products, and Pharmacovigilance during Breastfeeding: A Mixed-Methods Study on Women's Opinions. Journal of Human Lactation, 32(2), 324–332. https://doi.org/10.1177/0890334415619746

[2] https://www.fda.gov/media/124749/download

[3] Colaceci, S., Giusti, A., Chapin, E. M., Notarangelo, M., De Angelis, A., Vellone, E., & Alvaro, R. (2015). The Difficulties in Antihypertensive Drug Prescription during Lactation: Is the Information Consistent? Breastfeeding Medicine, 10(10), 468–473. https://doi.org/10.1089/bfm.2015.0086

[4] Giusti, A. & Colaceci, S. (2015). Breastfeeding and human lactation: the dark side of reproductive pharmacovigilance?

Safety of Medication Use in Pregnancy, EuroMediCat European Conference, Poznan, Poland, 2015

[5] Colaceci, S., Giusti, A., Chapin, E. M., Bettinelli, M. E., De Angelis, A., Zambri, F., … De Mei, B. (2017). E-learning to Improve Healthcare Professionals' Attitudes and Practices on Breastfeeding. Breastfeeding Medicine, 12(10), 629–636. https://doi.org/10.1089/bfm.2017.0060

[6] Colaceci, S., Zambri, F., D'Amore, C., De Angelis, A., Rasi, F., Pucciarelli, G., & Giusti, A. (2020). Long-Term Effectiveness of an e-Learning Program in Improving Health Care Professionals' Attitudes and Practices on Breastfeeding: A 1-Year Follow-Up Study. Breastfeeding Medicine, XX(Xx), 1–7. https://doi.org/10.1089/bfm.2019.0203

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement and https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.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: https://www.ema.europa.eu/en/documents/other/guidelines-good-pharmacovigilance-practices-introductory-cover-note-public-consultation-first-seven_en.pdf).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	PHARMIG the association of the Austrian pharmaceutical industry welcomes the opportunity to provide comments on the draft GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women. Please find our specific comments 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')*	Outcome *(To be completed by the Agency)*
46		Comment: In the current draft pregnant and breastfeeding women are considered vulnerable population. However, this may lead to misinterpretation and they can make well thought through decisions. "Pregnant and breastfeeding women are considered ~~vulnerable~~, or special populations,…."	
81 - 82		In spontaneous reporting, the term 'adverse event' is synonym to (suspected) adverse reaction and all birth defects are (suspected) 'serious adverse reactions' (see GVP Annex I). Comment: The wording is misleading because adverse event and adverse reaction are not the same. Proposed change (if any): Please consider different wording.	
95 - 96		Comment: Reference is made to the guideline: • CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: 93 from Data to Labelling (EMEA/CHMP/203927/2005	

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)*
		However, in the current draft there is a lot of duplication of information and tables from this guideline i.e. Annex 1 to 4 of the referenced guideline Proposed change (if any): Delete duplications	
117 - 119		Comment: It is mentioned exposure through semen which may lead to confusion during translations and interpretation between semen, sperm and seminal fluid which has different meanings. Only mutagenic or genotoxic substances may have an effect the sperm due to DNA damages. However, exposure can only be transferred via the seminal fluid. In addition a substance is teratogenic or a human teratogen or not, but it is not clear what is meant with a highly teratogencic substance. Proposed change (if any): Exchange "semen" throughout with "seminal fluid". Exposure through ~~semen~~ seminal fluid is another route of exposure to the embryo or foetus. Whether this carries a risk in clinical practice is unknown at present, but this should be considered for ~~highly~~ potent teratogenic substances that are transmitted into seminal fluid.	
142		Comment:	

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)*
		Throughout the document terminology is varying like birth defect (teratogenicity) or congenital anomalies etc. This should be aligned with the referenced guidelines and their definitions and one term should be used throughout Proposed change (if any): Instead of birth defects (teratogenicity) and other similar terms sometimes, the term "Congenital anomalies (birth defects)" should be used consistently throughout	
160		Comment: A substance is teratogenic or a human teratogen or not, but it is not clear what is meant by major teratogen activity. Proposed change (if any): It needs to be recognised that if a ~~major~~ teratogen mostly results in spontaneous implementation losses, pregnancy loss or stillbirth, then only evaluating the frequency of congenital anomalies (birth defects) would underestimate the teratogenic impact."	
189 - 192		Comment: Also other routes for PK data evaluation could be considered depending on the active substance exposed to and possible route of absorption (substance may not be absorbed in the gastrointestinal tract of the breastfeed	

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)*
		child due to normal composition (proteins, fat) of breastmilk resulting in a physicochemical interaction. Proposed change (if any): PK data in a child after intake of a medicine with breast milk provides some information about the possible risk to a child, and when an adverse reaction is suspected in a breastfed infant, it may be valuable to obtain a ~~blood~~ an adequate PK sample (ie blood, stool, urine) from the child.	
207		Comment: The term pregnancy loss and stillbirth is used in the draft guidance, but not specifically defined. Proposed change (if any): ***Pregnancy outcome***: End result of pregnancy, which includes ectopic pregnancy, miscarriage, foetal death, stillbirth, early pregnancy loss, termination of pregnancy and live birth.	
237 - 238		Comment: The current definition of: "***Foetotoxic effect****: Alteration of foetal growth, functional defects or* ***malformations*** *caused by a medicine or other substance and which may be transient or permanent*." is not consistent with guideline EMEA/CHMP/203927/2005. Foetotoxic effect, which includes effects such as growth retardation or adverse effects on either histological or functional maturation of	

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)*
		organs (the period of highest risk begins during the second trimester of pregnancy and continues throughout pregnancy). A malformative effect is a teratogenic effect for example. Proposed change (if any): align definitions with existing guidelines	
281 - 285		Comment: GVP Module V states that the absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern and only if a different safety profile can be expected. But the current sentence seems to imply that pregnancy and breastfeeding will be always missing information and not only when a different safety profile is expected. This may be misleading and would raise ethical considerations for a known teratogen for example as the missing information will hopefully never been completed as it may result in a disaster as in history and that is why a contraindication and a PPP exist in the SmPC for such active substances. Therefore, based on the available information a risk-based approach should be taken considering for example in-vitro and non-clinical findings in rodents and non-rodents for detected congenital anomalies (birth defects) in one or two species (resulting for example in an important identified risk in the RMP).	

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)*
		Proposed change (if any): This statement ~~is~~ may be applicable to pregnant and breastfeeding women, as they are rarely included in clinical trials (see P.III.A.1.1.).	
296 - 299		The RMP should specifically discuss the likelihood of use of the medicine in pregnancy, breastfeeding and women of child-bearing potential in the light of the indications, alternative treatment options, the need for effective contraception and the complexities of changing treatment if use during pregnancy is to be avoided. Comment: Risks of untreated disease for the woman and the unborn child when no medicine is used should be addressed Proposed change (if any):	
409		Comment: It should be considered that a non-interventional study in accordance to current legislation and guidances is defined as: that the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation; Therefore such a prospective non-interventional design may not be appropriate based on the information in the SmPC. See EMEA/CHMP/203927/2005	

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)*
		Appendix 3 [5] 5o [9] for which a non-interventional study would be feasible, for other product ie. with contraindication different design would be needed to considered as it would also imply that the routine RMM was not followed (ie. contraindication) and would mean to be strengthened resulting in less pregnancy exposure with congenital abnormality outcomes for example. Not all of these studies should be classified as post authorisation safety studies. Proposed change (if any): ***P.III.B.4. ~~Post-authorisation safety studies~~ Additional Pharmacovigilance Activities***	
410-411		Comment: See above Proposed change (if any): If applicable the requirements for the design and conduct of post-authorisation safety studies (PASS) in GVP 410 Module VIII should be followed,…….	
427		Comment: See above Proposed change (if any):	

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)*
		Carrying out ~~a PASS~~ an additional pharmacovigilance activity may be of particular value when use of a medicine is expected in pregnancy or breastfeeding, such as in the following situations:	
439		Comment: See above Proposed change (if any): If a ~~PASS~~ study based on pregnancy outcome parameters is considered warranted, it should be designed taking into account the issue of competing endpoints….	
451 – 453		Comment: PK studies would only be helpful if there is an indication that the PK may differ in a pregnant human being. Proposed change (if any): If use of a medicine during pregnancy is indicated and from all available evidence, there is no suggestion of harm, it may be appropriate in certain circumstances to evaluate the impact of pregnancy on medicine plasma levels in pharmacokinetic (PK) studies.	

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)*
471 – 473		Comment: The term medicines safety study may be misleading and is not needed in this context. Proposed change (if any): • ~~medicines safety studies:~~ Pharmacoepidemiological studies of adverse events of special interest in causal association with a medicine, taking into account the impact of the underlying maternal condition (i.e. non-exposed disease comparison group) and other potential confounders	
477 – 480		Comment: See comment on PASS Proposed change (if any): In other cases, if a drug utilisation study were to show usage in women of childbearing potential or in pregnant women to an extent that studying associated pregnancy outcomes would be warranted, then setting up ~~a PASS~~ a study with ~~safety~~ pregnancy outcome parameters ~~endpoints~~ should also be considered.	

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)*
543		Comment: See PASS before Proposed change (if any): The design and conduct of a ~~PASS~~ study in the population of pregnant women should take into account the specific characteristics of this population that may lead to confounding.	
560 - 561		Comment: See PASS before Proposed change (if any): Based on the guidance in P.III.B.4., for ~~PASS~~ additional pharmacovigilance activities in pregnancy, proposed study designs should specifically 560 address and justify:	
584		Comment: See PASS before Proposed change (if any): So far, ~~PASS~~ studies in breastfed children are very rare.	

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)*
680 - 682		Comment: See previous comment on term "semen" Proposed change (if any): • Where harm to the embryo or foetus by transfer through ~~semen~~ seminal fluid is an identified safety concern, minimising exposure via male partners exposed to the medicine by use of barrier contraception, avoidance of donation of sperm and informing the physician if the partner becomes pregnant;	
738 - 740		Comment: See previous comment on term "highly" or "major" teratogen Proposed change (if any): For ~~highly~~ potent teratogenic substances, the potential of exposure through ~~semen~~ seminal fluid should be considered and if an identified safety concern for exposure through ~~semen~~ seminal fluid exists, the recommendation to use barrier methods needs to be made.	

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)*
789 - 792		Comment: Text should be more flexible. Proposed change (if any): This appendix is copied from the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005) and provides a number of possible parental and neonatal data elements from which relevant points can be selected as applicable when establishing a questionnaire of pregnancy exposure to medicinal products.	
898 - 899		Comment: It should be more flexible to be established on new contraception for at least 3 weeks prior to pregnancy test and treatment initiation to be in accordance with existing SmPCs/Annex IID requirements for example for the human teratogen thalidomide (proven effective since more than 10 years) Proposed change (if any): **Any starter on new method contraception should have a repeat pregnancy test ~~at~~ after 3 to 4 weeks if there is any risk of pregnancy at start of contraceptive method**	

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)*
902 (table)		Comment: Table should be aligned with current approved SmPCs/Annex IID requirements for example for the human teratogen thalidomide (proven effective since more than 10 years) Proposed change (if any): Example of progesterone-only pills (i.e. desogestrel) and established user (more than 3 weeks), reliable and consistent user should move up to highly effective method and should not require an additional barrier method. Confirmed Tubal sterilisation as well as confirmed heterosexual abstinence are currently not considered or mentioned	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Quanticate (UK)

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: https://www.ema.europa.eu/en/about-us/legal/general-privacy-statement *and* *https://www.ema.europa.eu/en/documents/other/specific-privacy-statement-public-consultation-good-pharmacovigilance-practices_en.pdf*).

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1. General comments

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

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)*
225 to 226		Comment: Pre-term birth is clearly defined as less than 37 weeks of gestation. Is there a week of gestation that a premature birth should always be considered to be medically important (in the absence of any other serious events or outcomes in the baby) or should this be assessed on a case by case basis? Proposed change (if any): Maybe useful to provide some guidance on this bearing in mind that if the case is a spontaneous report it can be difficult to obtain follow up.	
318 to 319		Comment: Spontaneous reports should be followed to obtain the outcome of the pregnancy and on the development of the child after birth. Is there any guidance on how long after the birth of the child, the MAH should continue to follow up about the child's development? Proposed change (if any): Maybe useful to provide some guidance on this or define when it is acceptable to consider the case as lost to follow up.	
333 to 338		Comment: What is recommended for the route of administration for cases that don't lead to pregnancy loss or	

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)*
		other adverse pregnancy outcomes – should this be different to transplacental? Also what if the exposure occurs prior to conception? Should the reaction term "exposure in utero" be added only in the event of an adverse pregnancy outcome and not for pregnancy cases with a normal birth outcome? Proposed change (if any): Would be useful to provide further clarification	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<28 February 2020>

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Regeneron Pharmaceuticals, Inc.
[redacted] Ireland
[redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Regeneron welcomes the initiative by the Agency in releasing this Guideline on good pharmacovigilance practices (GVP) in pregnant and breastfeeding women and appreciates the opportunity to provide comments.	
	Regeneron acknowledges that pregnant and breastfeeding women are a particularly vulnerable population where risk-benefit considerations related to medicine use are usually more complex – and where serious unmet medical needs can be particularly challenging to address. We have a dedicated interest in exploring the safety of our products in pregnant/lactating women, as illustrated by our multiple pregnancy registries (e.g. dupilumab, sarilumab, alirocumab's registries), and remain committed to collecting high quality data that might help inform sound evidence-based decisions on the use of our medicines in these patients. We commend the Agency for publishing a draft guideline on this relevant topic.	

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)*
Lines 173-179		*"Typically, in the population of pregnant women there are limited numbers of exposure to a medicine; therefore, there will be an even smaller number of adverse pregnancy outcomes (…).This has implications for the numbers of spontaneously reported adverse events and on cases identified through post-authorisation surveillance methods, as numbers are expected to be small, making it difficult to identify an increase in cases of a rare adverse reactions. It also means 'birth defects' in general should not be studied as one single outcome."* The meaning of the statement that birth defects in general should not be studied as a single outcome is unclear. The Agency should clarify if it means that Sponsors should avoid using birth defects as a single outcome when designing clinical studies. Designing such a study is challenging as in most situations it is impossible to prespecify birth defects that should be investigated. Therefore, we request that the Agency include more specific suggestions addressing best practices Sponsors may incorporate in clinical trials in order to mitigate challenges in identifying increased incidents of rare adverse reactions of birth defects. A more detailed recommendation on this complex topic would help Sponsors design a study that complies with EMA's	

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		expectations and which generates high quality data on potential adverse pregnancy outcomes.	
Lines 315-319		*"Reports where the embryo or foetus may have been exposed to (a) medicinal product(s) (either through maternal exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth."* Regeneron agrees with the basis of the Agency's recommendation of collecting information on the development of a child after birth when the embryo or foetus has been potentially exposed to a medicinal product(s). However, as written, the guideline is not clear on the specific actions the EMA recommends should be undertaken in the follow-up period or what the Agency would deem as an acceptable timeframe for follow-up. More detailed guidance around these topics would better inform Sponsors of the Agency's expectations and support increased compliance and follow-up from Sponsors for these cases.	
Lines 511-515		*"Although retrospective enrolment [in registries] may introduce bias, information entry after the pregnancy outcome is known can still be valuable. Therefore,*	

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		although prospective enrolment is preferred and should be encouraged, women who wish to enrol retrospectively should not be discouraged to do so and their pregnancy outcomes should be included in the study report. The retrospective nature of such data needs to be accounted for in the analysis (…)" While we recognize the importance of recording pregnancy outcome information in the most comprehensive manner, the Agency should recognize that retrospective data will likely introduce more bias, as reporting is more likely to occur following a negative outcome. Therefore, we would encourage the Agency to explicitly acknowledge this consideration. Further, we request that the Agency consider recommending that retrospectively collected cases should be examined separately rather than pooled into an analysis which also includes prospective data.	
Lines 616-665 Section *P.III.B.6. Safety communication*		At present, some of the recommendations discussed in Section *P.III.B.6. Safety communication* overlap with those in the following section of the guidance (*P.III.B.7. Risk minimisation measures*). Risk minimisation measures (RMM), for example, are discussed in both sections, which could lead to some confusion. Regeneron suggests that the EMA clearly distinguish between what is considered 'safety communication', which we interpret to be general good	

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		practice for all medicines, from actual RMM, which are not always imposed and are usually reserved for medicinal products associated with safety risks. We encourage the Agency to clarify these differences in the appropriate sections of the guideline and consolidate commensurate recommendations in their respective sections. We believe that our suggestion would help minimize any ambiguity associated with including Agency recommendations on each topic within these two distinct sections, thereby increasing Sponsors' understanding of the Agency's recommendations.	
Lines 666-694 Section *P.III.B.7. Risk minimisation measures*		Following from the preceding discussion, we believe that Section *P.III.B.7. Risk minimisation measures* should clearly explain that RMM do not apply to all medicines but are reserved to those deemed as being associated with particular risks. We suggest the Agency to consider moving the statements from lines 690-694 to the beginning of this section, to clearly establish the role of RMM and in which instances they should be implemented. These changes would boost Sponsors understanding of the Agency's recommendations, and help ensure increased compliance to them. Proposed changes: Please consider the following revision:	

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		"P.III.B.7. Risk minimisation measures *In the area of pregnancy and breastfeeding, the objective of risk minimisation measures (RMM) generally is to reduce any risk to the child as much as possible given the need for appropriate treatment for the mother.* *When serious risks of a medicinal product with use in pregnancy have been identified, a set of stringent RMM should be implemented aiming at avoiding exposure in utero, including sometimes a PPP (see P.III.B.7.2.). For less serious risks, the emphasis will be on ensuring that healthcare professionals and patients have information available supporting them making informed decisions regarding the most appropriate choice in the individual case.* *~~In this area,~~ ~~s~~ Strategies for RMM include those aiming at: (…)"* And please consider the following revision: *"(…) - In breastfeeding women, depending on the therapeutic context and the availability of therapeutic alternatives, avoiding use of medicines that significantly reduce breast milk production.*	

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		~~*When serious risks of a medicinal product with use in pregnancy have been identified, a set of stringent RMM should be implemented aiming at avoiding exposure in utero, including sometimes a PPP (see P.III.B.7.2.). For less serious risks, the emphasis will be on ensuring that healthcare professionals and patients have information available supporting them making informed decisions regarding the most appropriate choice in the individual case."*~~	
Lines 771-784 Section *P.III.C.2. Post-authorisation safety studies in the EU*		Regeneron appreciates EMA's intent in referencing organisations that compiled lists of data sources available to support the conduct of post-authorisation safety studies (PASS). However, we believe that the Agency could enhance the value of this guideline by adding a list of reference data sources to the Appendices. A new Appendix could help Sponsors find information on relevant data sources more easily and leverage it when conducting PASS in the EU.	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 February 2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
Seattle Genetics

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Guidance is well written and provides useful information and clarification on the topic of this Guidance.	

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)*
735		Comment: we would recommend that the guidance include the FDA guidance on Reproductive Tox Testing and Labelling Recommendations, with regard to the duration of contraception in male and female patients to minimize risk to a developing embryo or fetus. Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27-February-2020

Submission of comments on GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA/653036/2019)

Comments from:

Name of organisation or individual
UCB

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1. General comments

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

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)*
46		Comment: In line with US DHHS (45CFR46 update July 2018) women of child bearing age are not considered as vulnerable population. Proposed change (if any): women are considered ~~vulnerable, or~~	
54-55		Comment: We consider that in all cases, when a women is taking a drug during pregnancy, the benefit and risks need to be evaluated for both the women and the unborn. Proposed change (if any): ~~Except for situations where a medicine used during pregnancy specifically aims to benefit the (unborn) child~~ In all cases, risk-benefit considerations regarding the medicine use before or during pregnancy or breastfeeding differ from other medicine use.	
56		Comment: As mentioned later in the document the treatment of the mother disease could be beneficial for the unborn. Therefore it is appropriate to discuss both the risk for the unborn and the benefit Proposed change (if any):	

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		the potential risks and benefit to the (unborn) child also need to be taken	
69-70		Comment: It's still challenging to obtain valuable data in this population Proposed change (if any): ~~it is becoming increasingly feasible to access data and generate knowledge on safety in this population~~	
Lines 126-134, 677-679		Comment: Physiological fluctuation due to pregnancy of the treated disease activity (physiologically expected worsening or improvement), and the need for adjusting medicinal treatment strategy or regimen is also an important factor for evaluation Proposed change (if any): Some words can be added to address the importance of generating such data and assessing the impact on the treatment strategy and risk mitigation.	
Line 333-335		Comment: "Exposure in utero' is not a MedDRA term (The closest one is 'Drug exposure in utero)'. Could you please clarify which MedDRA term you are expecting and if MedDRA Point to Consider is acceptable to follow for coding of pregnancies? The coding with other LLTs could bring more granularity when analyzing	

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		pregnancies (maternal versus paternal exposure, before or during pregnancy,…) Proposed change (if any):	
Line 336-338		Comment: Could you please confirm that is acceptable to follow MedDRA Point to Consider for coding of breastfeeding exposure? Proposed change (if any):	
571-593		Comment: This § do not provide the same decision tree on when you should consider the PASS for breastfeeding women, while we consider that this need should be assessed based on similar decision tree (e.g. should a drug be used for a disease occurring in women of childbearing age, a PASS should be added in the RMP). Proposed change (if any):	

Please add more rows if needed.