**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** |

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*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)* |
| --- | --- | --- |
|  | 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. * “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.  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 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.** |  |

1. 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)* |
| --- | --- | --- | --- |
| 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 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.  **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):**  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:   1. 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; 2. 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.  **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 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 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 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.**” |  |
| 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](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf) - ANNEX 4 - DEFINITIONS) stated 12 weeks as the end of the period of organogenesis. Current text states 16 weeks.  **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 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):**  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):**  “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”.  **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.  **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.” |  |
| 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 completed37 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 **more than 1,499 grams and** less than 2,500 grams (**between 1,500 and** ~~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.  **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. |  |
| 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 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 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. |  |
| 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. |  |
| 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.” |  |
| 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.  **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 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:**  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    cid:image003.jpg@01D5D054.A9583C20 |  |
| 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**  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. |  |
| 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.  **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 |  |
| 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. |  |
| 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 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. |  |
| 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 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”. |  |
| 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; |  |
| 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. |  |
| 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)**:  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**:  “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 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. |  |
| 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. |  |
| 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. |  |
| 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)**:  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 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):**  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. |  |
| 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?  **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. |  |
| 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, 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) |  |
| 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 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 C~~umulative 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  **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.  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]** |  |
| 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 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). |  |
| 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):**  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 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** ~~Ee~~ffective methods”. |  |

Please add more rows if needed.