Submission of comments on 'Concept paper on revision of the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling'

Fields marked with * are mandatory.

* Name of organisation or individual

EFPIA

* Country of organisation or individual

Belgium

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

Please click **here** to be redirected to the guideline text. The public consultation is launched on 2 May 2024 until 31 August 2024.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section. Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 31 August 2024) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EMA Privacy Statement

All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.

This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller. HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.

For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

You have the right to access and receive a copy of your personal data processed, as well as to request rectification or completion of these data. You may also request erasure of the data or restriction of the processing in accordance with the provisions of Regulation (EU) 2018/1725. You can exercise your rights by sending an e-mail to Datacontroller.HumanMedicines@ema.europa.eu.

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You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.

- (●) Yes
- ( ) No

Should you not want to give consent to publish, please send your objections to Datacontroller.HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

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1. General comments

	General comment
1	EFPIA greatly appreciates the well written concept paper, offering additional information on revision of the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling. We welcome the opportunity to submit comments and hope they will help in improving the guideline with greater clarity.
2	It is recommended to expand the scope to a guideline on data “planning”, in order to aid clinical development programs, and risk evaluation criteria, whereby any risks identified during a risk assessment are then weighted and put into context of a general risk-benefit balance ie. “Guideline on Risk Assessment and Evaluation of Medicinal Products on Human Reproduction and Lactation: from Data Planning to Labelling”. Text proposed for addition “Evaluation” and “Planning”.
3	Upon reading the entire document it appears that this concept paper aims to define the scope of a planned update of the existing guidelines, however this is not stated. It would be good to clarify the objective and scope (e.g. post-marketing only?) of this concept paper in a dedicated section.
4	Adding post-authorisation safety activities for pregnancy and lactation (such as studies, enhanced pharmacovigilance, registries) would bring value to the updated legislation. Some guidance is given in GVP VIII and in GUIDELINE ON THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY: NEED FOR POST-AUTHORISATION DATA, however more guidance is needed on when each type of activity should be conducted. Registries remain the most prevalent activity, however their efficiency in collecting valuable information in pregnancy and breastfeeding has been questioned in various publications.
5	It is encouraging to see that this document addresses the ICH E21 “Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials“ activity and the need to start earlier with data generation for this specific population. The EU R&D framework needs a setup that encourages involvement of pregnant women or those of child-bearing age in clinical trials and on tools allowing for their involvement. This aspect is missing in this guidance that considers the approach from data planning to labelling. Thereby, the document would not only focus on assessing risks and safety but be more inclusive considering how data can be generated for this population and decision makers.

6	It is recommended to align with the soon to be published guidance from the Innovative Health Initiative ConcePTION project, which will provide guidance on animal models for lactation and pathways for documenting developmental delay through standardized apps and the IMI ConcePTION proposed Core Data Elements: Core Data Elements for Pregnancy Pharmacovigilance Studies Using Primary Source Data Collection Methods: Recommendations from the IMI ConcePTION Project - PubMed (nih.gov). https://pubmed.ncbi.nlm.nih.gov/36976447/
7	It is recommended to consider aspects focusing on risk-benefit considerations for pregnant or nursing women with severe or rare diseases discussed in the new guideline from FDA, due to be updated by end of 2024 (FDA Enhancing Clinical Study Diversity Workshop Report | November 29 and 30, 2023 and FDA Rare Disease Innovation Hub to Enhance and Advance Outcomes for Patients | FDA), to ensure EMA proposal is up to date. An 'integrated risk assessment' approach, similar to the method used for non-standard QT assessment, would be a suitable alternative for addressing this issue. This approach would involve preclinical and early clinical data, along with data from clinical studies supplemented by potentially real-world or registry post-approval data. Furthermore, such an approach would allow for ongoing updates based on recent and continuously available new information, such as that from the increasingly available new modalities. https://www.fda.gov/media/179261/download https://www.fda.gov/news-events/fda-voices/fda-rare-disease-innovation-hub-enhance-and-advance-outcomes-patients
8	The current guideline provides limited guidance regarding the recommended use of pregnancy testing and contraception in women of childbearing potential (WOCBP) and their male partners. In fact, the examples of SmPC statements do not include any recommendations on pregnancy testing or contraception for male partners. Additionally, the guideline does not define what is considered an effective contraception method or provide parameters/thresholds for classifying contraception methods. Recommendations on when a highly effective method or a dual method is required are also missing. These pieces of information should be included in the updated guideline.
9	We request the Agency to consider adding the 'GUIDELINE ON THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY: NEED FOR POST-AUTHORISATION DATA (2005)' to the list of relevant guidelines for alignment, since this guideline has several important considerations for active surveillance and collecting post-authorization data in pregnancy.

10	In addition to the proposed updates, it may be helpful to present the risk with more emphasis on the context of benefit (i.e., life-saving vs life-style product, availability of safer alternatives) and target population (i.e., probability of exposing WOCBP, fetus/child or potential father, based on indication and potential for off-label use)). This may help guide sponsors/MAHs to adopt a risk-based approach to the design of (non-)clinical studies as well as post marketing studies and programs, with the objective to increase the collection of human data regarding pregnancy and lactation as early as possible (link with ICH E21 Concept Paper).
11	It would be appreciated to have more and clearer guidance on how to communicate risk and benefits for the mother and child in labelling and it is well understood that the core of the issue lies in the limitations of the quantity and quality of the data that exists. When composing wording to support HCPs and patients in making informed decisions, the patient voice becomes important. Particularly, the aspect of how the used language is understood by HCPs and patients and the impact on their decision-making needs consideration before proposing a standard for the Package Leaflet (PL). However, template language (i.e. standardized text for the SmPC) may not fit appropriately for complex integration of data. Risk-benefit decisions regarding use of a drug during pregnancy are more complex than a standard statement suggests, and reliance on such statements by HCPs could result in inadequately informed clinical decision making. A change in this concept is therefore proposed with a clear ask to present the data in a descriptive/ factual way, with any limitations acknowledged in the text for transparency. This approach would be similar to the FDA Pregnancy and Lactation Labelling Rule (PLLR), allowing for narrative summaries of the risks of a drug during pregnancy and discussions of the data supporting those summaries to be included in labeling, to provide more meaningful information for HCPs. In such a combined approach, all relevant data are available to the decision-making HCPs in the SmPC as well as appropriate language for the patients in the PL. If the GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING is revised in ways such that the SmPC is impacted, it is recommended to assess impact, if any, to the QRD template. In particular, assess impact to annex I (SmPC) and Package Leaflet (annex IIIB) in QRD template.
	For nonclinical pregnancy data, there are number of situations where a NOAEL is not defined, specifically either in studies conducted with non-human primates with biopharmaceuticals and intended to be used for hazard

12	identification [as per ICH S6(R1) Guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals] or in the case of using a species-specific surrogate molecule in a rodent or rabbit [as per ICH S6 (R1) and ICH S5(R3) Guideline on detection of reproductive and developmental toxicity for human pharmaceuticals]. It is suggested to add at least a sentence acknowledging the value and relevance of these hazard-identifying studies, even if a NOAEL cannot be determined for the clinical candidate.
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2. Specific comments on text

2.1. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	26-35	The decision scheme and advice on SmPC wording is very strongly aimed at molecules where a risk has been identified in the nonclinical testing and this risk needs to be contextualized. Where there are no effects detected in reproductive testing, the suggested text only covers malformations. It does not address the full range of endpoints evaluated in reproductive studies and where there is no evidence of adverse findings. Additional information on how those situations should be managed and communicated to the patients and/or HCPs is needed. Therefore, it is suggested to update the guidance to include risk assessment when there are no adverse findings in the reproductive toxicity testing.	
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2.2 Problem statement

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	42	Information to be included in the PL. The scope of information to be available for the patients' needs to be defined to make it fit for purpose and easily understandable. Please refer to general comment 11 for further information.	
2	46-48	Using the term "such data sources" is confusing. It is unclear as to what data sources the reference pertains to, therefore clarification would be helpful. Text proposed for addition: "and observational data sources including", "electronic healthcare records, administrative claims and other existing data sources"	"Most data regarding human pregnancy exposures are collected after marketing authorisation by spontaneously reported post-authorisation data, and observational data sources including patient/pregnancy registries, electronic healthcare records, administrative claims and other existing data sources, and via epidemiological studies undertaken in such data sources [7]."
3	47	We would appreciate if the document was updated with guidance for companies using publicly available data on pregnant women and infants, including stipulations for data sharing.	
4	53-58	Guidance should also address Pregnancy PK data and placental transfer PK data in addition to breast milk.	
5	59-63	Clarification is appreciated if new approach methods (NAM) encompass e.g. in-silico trials, mathematical models of placental transfer.	
		A brief description of the NAMs and the Agency's openness to use of NAMs available in the future would help in better understanding of how to incorporate use	

6	62-63	of alternatives to animal testing regarding reproductive toxicity. A reference to the need for NAMs to be Fit-for-Purpose, so that some level of validation has been conducted is needed and any relevant guidelines /guidelines should be referenced. There also needs to be some guidance on when evaluation using NAMs DART studies would be appropriate? Should NAMs DART studies be conducted in conjunction with existing non-clinical studies, or are there cases where evaluation can be done based solely on NAMs DART studies depending on the situation? It is also not clear whether use of a NAM(s) will be used to inform the SmPC or PL, either fully or partially i. e. does the NAM need to be validated to recapitulate a pregnancy with all its attendant components such as maternal and fetal influences in an integrated manner and that can be related to exposure, or can NAMs be used to support certain aspects of the pregnancy as a whole? What guidelines should be referenced when conducting NAMs DART studies (e.g. Essential considerations for successful qualification of novel methodologies, etc.)?"	
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2.3 Discussion (on the problem statement)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	65	Suggest adding the ENCEPP guidance as a source to utilize for consistency. http://www.encepp.eu/structure /documents /Data_sources_for_medicines_in_pregnancy_research. pdf	
2	65-66	No ethical values or guidelines are referred to in this Concept Paper. Although it is not entirely clear if the scope of this Concept Paper includes clinical safety data collected during clinical trials, this could be at least achieved by making references to the principles described in the CIOMS International Ethical Guidelines for Health-related Research Involving Humans, specifically to Guidelines 18 and 19 (WOMEN AS RESEARCH PARTICIPANTS and PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS).	
3	65-80	This guideline is (in general) solely aimed at small molecule pharmaceuticals, and does not cover large molecules, such as biotherapeutics or more novel modalities, such as gene therapies, anti-sense oligonucleotides, mAb derivatives etc. It is proposed to include reference to ICH S6(R1) “Preclinical safety evaluation of biotechnology-derived pharmaceuticals” on biopharmaceuticals and the different reproductive testing paradigm for these molecules. Additionally, include references to other guidelines on the other newer modalities.	

		Although it is hoped all modalities are in scope of this document, if it is a deliberate intention not to cover these modalities, then this needs to be specifically stated.	
4	65-81	Cross-alignment and cross-reference to the guidance documents mentioned is welcomed. Especially, the first two guidelines include valuable information with respect to pregnancy prevention not yet adequately covered in the current guideline in scope.	
5	81	The guidance should present the risks without omitting the benefits for the mother and the baby to allow the prescriber and the patient to take informed and well-balanced decision.	
6	82	Ensure all terminologies are aligned with the relevant guidelines and recommendations. There are some that are not currently listed (e.g., congenital anomaly /congenital abnormality).	
		Teratogenic effects/teratogenicity/embryotoxicity are not clearly defined. Consider inclusion and clarification in referred guidance to first trimester exposure and administration, currently not included (namely on regulatory expectations for monoclonal antibodies on posology and PK supportive data). The concept paper mentions that in the current guideline malformations are the only key marker of harm addressed and that second and third trimester	

7	82-92	exposure effects on potential outcomes are not yet adequately covered. This notion is also welcomed and further elaboration on these topics would be appreciated (including discussion on robust embryology and potential outcomes). As part of expanding the impact of drug exposure to 2nd and 3rd trimesters and corresponding adverse pregnancy outcomes, it would be helpful if the EMA could provide clarification what is considered as clinically meaningful for the prospective pregnancies with appropriate exposure and known outcome required for label update. 'Key adverse pregnancy outcome' should not be limited to malformative events and effects on fetus only. Current guideline and this concept paper limits adverse pregnancy outcome considerations only to effects on the fetus; for HCPs and patients it is equally important to understand the impact of IMP on pregnancy and mother. ie., miscarriages, hypertension, gestational diabetes etc. This type of information can be obtained from clinical trials with limited numbers of pregnant individuals being enrolled where the data will be of high quality. Collection of this type of safety data should also be given consideration as well. Please include additional subtopic for Maternal and Pregnancy outcome.	Please consider clarifying that the "types of abnormalities that are typically associated with teratogenesis include embryonic or fetal death; morphological, functional and/or neurobehavioral abnormalities; and decreased growth rate and/or birth weight". References: T.J. Evans Reproductive toxicity and endocrine disruption R.C. Gupta (Ed.), Veterinary Toxicology: Basic and Clinical Principles, Elsevier Academic Press, New York (2007), pp. 206-244 J.M. Rogers, R.J. Kavlock Developmental toxicology C.D. Klaassen (Ed.), Casarett & Doull's Toxicology: The Basic Science of Poisons (7th edition), McGraw-Hill, New York (2008), pp. 415-486
8	93-104	This paragraph describes the potential use of weight of evidence for products within a class of known developmental toxicants based on the pharmacological effect. There should be a similar discussion on whether a similar weight of evidence can be used for	

		products which are known not to cause developmental toxicity based on the pharmacology, particularly for biotherapeutics where off-target toxicities are rare.	
9	93-10	In addition to NAMs and weight of evidence approach based on class of known developmental toxicants, consideration should also be given to application of data from less frequently used animal models such as non-human primate (NHP) and other non-routine models, including rodent administered a surrogate test article, and transgenic animals. With evolution of new modalities (large molecules, oligonucleotides), increased species specificity, and efforts to minimize use of NHP for nonclinical reproductive testing, the need for NHP or alternative animal model use will increase. It would be useful to include some consideration of data application to risk assessment. For example, in which scenarios the data is appropriate for hazard identification only versus calculation of safety margins and risk assessment.	
10	99-102	We suggest the guideline revision addresses the labeling implications when weight of evidence or alternative approaches are used. This would help in clarifying if these approaches are considered to have similar robustness for characterizing risk as a nonclinical toxicology animal study(ies).	
11	100-101	The added example ‘based on the pharmacological effect (e.g. anti-PD/L1)’ seems unnecessarily specific, especially since there are already examples in this class of marketing approvals without nonclinical pregnancy data.	Suggest to remove ‘based on the pharmacological effect (e.g. anti-PD/L1)’.

		Text proposed for removal: based on the pharmacological effect (e.g. anti-PD/L1)	
12	105	Although this Concept Paper seems to address patients and HCPs call for access to more information on the safety of medicines in pregnancy and breastfeeding, only the SmPC and PL are being considered as possible solutions. However, just as new nonclinical and clinical methods enhance the early detection of potential reproductive risks, new digital systems allow more effective and user-friendly communication of the same.	Please consider adding under “Other topics” the use of digital tools for the communication of reproductive risks to patients and HCPs.
13	105 – 111	The intent behind the list of other topics is not fully clear - it could easily result in a substantial expansion of the requested nonclinical studies and/or substantially limit or markedly delay the approvability of some new therapeutics. Please clarify the intent of the ‘other topics’- are these areas that require additional nonclinical or clinical data prior to marketing approvals? Or areas of interest for post-marketing monitoring with ‘for cause’ label adjustments?	
14	105-120	One important challenge is the collection of data in rare diseases. This should be addressed in this guidance and more specifically in the sample size considerations for the clinical study power. Text proposed for addition: “Collection of data in rare diseases”	Add the following bullet point after line 120 “Collection of data in rare diseases”

15	106	Please clarify whether under “other topics”, other adverse developmental outcomes will be considered when reviewing guidelines, e.g., structural abnormalities, functional impairment and/or alternations to growth.	
16	106-107	Clarification on when to collect long term outcomes based on trimester of exposure and biological plausibility would be helpful. It may be feasible if this is limited to early years and neurodevelopment, but longer Follow-up may be logistically difficult and prone to many confounders as children grow in most regions. Children are only followed up routinely during early years. Please clarify the scope of long-term child outcomes and make clear expectations for post-marketing monitoring.	
17	108-109	Vaccination will always be dependent on national regulations therefore it is difficult to give standardized recommendations. Consider referring to national guidelines for vaccination of infants after in-utero exposure to immunomodulating or immunosuppressive medications.	
18	110	Consider adding transgenerational effects, if relevant.	
19	112	Clarification on, whether this causality assessment is regarding causality assessments on individual cases or causal inference of the total body of evidence, would be appreciated.	

20	113	Although not stated, perhaps clarify that “causality assessments of signals of reproductive adverse effects” will include both male and female adverse effects on pregnancy testing, contraception, fertility (reduced fertility and/or sterility) and any other adverse effects such as decreased lactation. Perhaps this is the input for wording in the SmPC (beginning line 127). Text proposed for addition: “on pregnancy testing, contraception and fertility in males and in females”	“…causality assessment of human reproductive adverse effects on pregnancy testing, contraception and fertility in males and in females should be considered…”
21	115	Practical guidance should be given for the case of older active substances that have no pregnancy registry, and where the clinical data rather consist of multiple literature studies, with sometimes quite some data (> 300 or 1000 pregnancies) but not prospectively collected.	
22	115-118	It is recommended to include other pregnancy risks (e. g. hypertension, abortions, gestational diabetes) in the study power calculations. Additionally, consideration should be given for including this type of information collected from these high-quality trials in the SmPC or PL.	
23	121	Current guideline does not discuss useful information that could be obtained from properly designed juvenile toxicology studies that could inform on the impact of a drug on the breastfed infant. It is recommended to address this gap.	
24	121	It is recommended to clarify the expectations towards infant data collection.	

25	121 – 126	It is suggested to add considerations for class effects in risk assessment, e.g. with monoclonal antibodies that are administered after the neonatal period of colostral immunoglobulin transfer. In general, IgGs are not present in high amounts except in colostrum, and systemic exposure of the nursing infant after that neonatal period is expected to be low due to protein digestion and limited absorption. Not all of these features are fully replicated in animal studies, but they should be considered for humans. Consider adding a note of the relevance of class effects in humans regarding periods of potential lactational exposure and effects on infants while acknowledging that lactational exposure will vary according to species.	
26	132	It is proposed for the SmPC text to integrate recommendations from CMDh press release dated July 2021 on active substances with genotoxic potential - Report from the CMDh meeting held on 20-21 July 2021 (hma.eu) https://www.hma.eu/fileadmin/dateien /Human_Medicines/CMD_h_/CMDh_pressreleases /2021/07_2021_CMDh_press_release.pdf	
27	132	Standard texts of warnings for outer (and inner) packaging, including pictograms, should be proposed for active substance with the most severe pregnancy outcomes (eg retinoids, valproic acid etc).	
		Along with improving information to HCPs and patients, standard text should be created to increase awareness	

28	132	regarding adverse event reporting, data collection (eg, registries, reporting to MAH) and information on exposures and normal pregnancy outcomes in SmPC and PL.	
29	132-135	Template language (i.e. standardized text for the SmPC) may not fit appropriately for complex integration of data. Risk-benefit decisions regarding use of a drug during pregnancy are more complex than a standard statement suggest, and reliance on such statements by HCPs could result in inadequately informed clinical decision making. A change in this concept is therefore proposed with a clear ask to present the data in a descriptive/factual way, with any limitations acknowledged in the text for transparency. This approach would be similar to the FDA Pregnancy and Lactation Labelling Rule (PLLR), allowing for narrative summaries of the risks of a drug during pregnancy and discussions of the data supporting those summaries to be included in labeling, to provide more meaningful information for HCPs.	
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2.4 Recommendation

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	133	Standard statements could be replaced with succinct statements which describe the data accrued, to allow the physician and patient to have a benefit/risk discussion. For medications used to treat conditions with no or few other alternative treatments available and when treatment cannot be delayed until the pregnancy has ended (for example), providing more information in a narrative form would be useful for HCPs when prescribing for and counseling patients. This comment would help address the following problem statement from the concept paper (section 2, lines 38-41): “The lack of clinical data on medicines safety for human fertility, during pregnancy and breastfeeding has long been highlighted as an area of public health need [4], and patients and healthcare professionals have expressed the need to have access to more information on the safety of medicines during pregnancy and breastfeeding [5].” This would also align with EMA’s commitment to “advance access through better understanding and communication of benefits, risks, and uncertainties of medicines use in pregnancy and breastfeeding, throughout the product lifecycle” (per section 2 of the concept paper, lines 43-45). As an example, when no increased rate of malformation is identified based on less than 300 prospective exposed pregnancies, the current guidance (2008) recommends that the following statement be included in section 4.6: “There are no or	

		limited amount of data (less than 300 pregnancy outcomes) from the use of {Active substance} in pregnant women" [see Labeling Example (5) in Appendix 3], with no further details included on the actual data generated. The revised guidance should allow to include brief summary findings based on limited data (< 300 pregnancy outcomes) in the above scenario (no malformative or feto/ neonatal toxicity observed) provided the limitations of the data and any caveats are clearly mentioned in the text for transparency.	
2	136-140	The current focus of the document is on the assessment of the risk but is not providing sufficient guidance how to achieve better data and better communication to patients for their individual decision making. The future guidance is recommended to take a broader view into account.	
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2.5 Proposed timetable

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	142	An ICH Working Group has also been started assessing pregnancy and lactation assessment for novel pharmaceuticals “ICH E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials”. It is strongly recommended that both guidelines are aligned.	
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2.6 Resource requirements for preparation

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	142	An ICH Working Group has also been started assessing pregnancy and lactation assessment for novel pharmaceuticals “ICH E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials”. It is strongly recommended that both guidelines are aligned.	
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2.7 Impact assessment (anticipated)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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2.8 Interested parties

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	148-157	Under the current scope, the guideline will only be applicable to low molecular weight pharmaceuticals. It should be seriously considered whether to expand this guideline to other modalities, particularly biotherapeutics particularly biotherapeutics, such as mAbs, vaccines, cell, and gene therapies.	
2	148-157	Under the current scope, the guideline will only be used where there is evidence of reproductive toxicity in the nonclinical testing. It is very important that this is expanded to cover molecules where no such toxicity is observed and whether there would be an expectation of a certain safety margin to claim that no evidence of adverse effects on pregnancy have been shown.	
3	151-152	As currently proposed, the guideline will provide information on how to communicate potential or identified risks. However, since risks could also be unknown, it is proposed to update the guideline accordingly (see proposed wording). Text proposed or addition: “unknown”	“The guideline will provide information on how to communicate unknown, potential or identified risks, specifically through the SmPC and PL”.
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2.9 References to literature, guidelines, etc.

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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Other comments

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
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Thank you for your contribution.

Contact

Contact Form