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2 EMA/CHMP/170670/2024  
3 Committee for Medicinal Products for Human Use (CHMP); Pharmacovigilance Risk Assessment Committee  
4 (PRAC)

5 **Concept paper on revision of the Guideline on Risk**  
6 **Assessment of Medicinal Products on Human**  
7 **Reproduction and Lactation: from Data to Labelling**  
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Agreed by Committee for Medicinal Products for Human Use (CHMP); Pharmacovigilance Risk Assessment Committee (PRAC)	April 2024
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Start of public consultation	2 May 2024
End of consultation (deadline for comments)	31 August 2024

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10 The concept paper proposes to revise the Guideline on Risk Assessment of Medicinal Products on  
11 Human Reproduction and Lactation: from Data to Labelling (EMA/CHMP/203927/2005)

12 Comments should be provided using this EUSurvey [form](#). For any technical issues, please contact  
13 the [EUSurvey Support](#).

Keywords	<i>Pregnancy, breastfeeding, lactation, fertility, reproductive toxicity, teratogenicity, contraindication, clinical assessment, non-clinical assessment, risk assessment, labelling, Summary of Product Characteristics (SmPC).</i>
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## 16 **1. Introduction**

17 The PRAC and CHMP work plans for 2023 [1,2] list several activities intended to implement guidance  
18 on “Special populations and products”. This includes further optimising close cooperation between  
19 these two Committees for the revision of the ‘CHMP Guideline on risk assessment of medicinal products  
20 on human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005)’ [3]. This  
21 concept paper outlines the areas in this guideline which are planned to be updated. This has been  
22 developed by a drafting group involving members from CHMP, PRAC, Non-clinical working party  
23 (NcWP), 3Rs working party (3RsWP), Quality review of documents working party (QRD) and Healthcare  
24 professionals working party (HCPWP). Representatives from the Patient and consumers working party  
25 (PCWP) have been invited and intend to contribute at a later stage of the guideline revision.

26 The current guideline provides guidance on the integration processes of clinical and non-clinical data  
27 for the assessment of the risk of adverse maternal, fetal or child effects in humans, as well as effects  
28 on fertility. Further, there is guidance on how to communicate the potential or identified risk through  
29 the Summary of Product Characteristics (SmPC).

30 A decision scheme to determine whether a medicinal product should be contraindicated during  
31 pregnancy is also included. Examples of standardized text for the SmPC are given for  
32 recommendations on the use during pregnancy and breastfeeding.

33 Wording regarding pregnancy and breastfeeding included in the SmPC and PL is intended to help  
34 healthcare professionals and patients making individual decisions about using a medicinal product  
35 during pregnancy and breastfeeding, and actions to take in case of unintended exposure.

## 36 **2. Problem statement**

37 At time of marketing authorisation, often only non-clinical data is available to provide information on  
38 fertility, pregnancy and breastfeeding in the SmPC and PL. The lack of clinical data on medicines safety  
39 for human fertility, during pregnancy and breastfeeding has long been highlighted as an area of public  
40 health need [4], and patients and healthcare professionals have expressed the need to have access to  
41 more information on the safety of medicines during pregnancy and breastfeeding [5].

42 Currently, the guideline does not provide corresponding standard texts for the Package Leaflet (PL).

43 In its Regulatory Science Strategy to 2025 [6], the EMA highlights their commitment to advance  
44 access through better understanding and communication of benefits, risks, and uncertainties of  
45 medicines use in pregnancy and breastfeeding, throughout the product lifecycle.

46 Most data regarding human pregnancy exposures are collected after marketing authorisation by  
47 spontaneously reported post-authorisation data, in patient/pregnancy registries, and via  
48 epidemiological studies undertaken in such data sources [7]. Such data sources are available in the  
49 EU, as compiled by the European Network of Centres for Excellence in Pharmacovigilance and  
50 Pharmacoepidemiology (ENCePP)<sup>1</sup>. The desire to obtain relevant data as early as possible in the  
51 product life cycle is being addressed through an International Council for Harmonisation of Technical  
52 Requirements for Pharmaceuticals for Human Use (ICH)<sup>2</sup> initiative.

53 Human breastfeeding information in the SmPC and PL often derives from pharmacokinetic evaluations  
54 (e.g. bioavailability), from animal studies (e.g. radiolabelled distribution studies) and clinical  
55 experience, generally obtained post -authorisation. Human studies on substance transfer into breast  
56 milk are still rarely submitted within marketing authorisation applications. The development of

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<sup>1</sup> [http://www.encepp.eu/structure/documents/Data\\_sources\\_for\\_medicines\\_in\\_pregnancy\\_research.pdf](http://www.encepp.eu/structure/documents/Data_sources_for_medicines_in_pregnancy_research.pdf)

<sup>2</sup> [https://database.ich.org/sites/default/files/ICH\\_E21\\_Final\\_Concept\\_Paper\\_2023\\_1106\\_MCAproved.pdf](https://database.ich.org/sites/default/files/ICH_E21_Final_Concept_Paper_2023_1106_MCAproved.pdf)

57 physiologically based pharmacokinetic (PBPK)-modelling approaches may facilitate the prediction of  
58 drug exposure in breast milk based on scarce data.

59 Since the adoption of the guideline in 2008, several developments in the non-clinical field of  
60 reproductive toxicology have taken place which have an impact on the interpretation of non-clinical  
61 data in relation to use of medicines during pregnancy and breastfeeding. This includes more guidance  
62 on interpretation of animal to human exposure margins and the possibility to use new approach  
63 methods (NAMs) as alternatives to animals testing, among others [8,9].

### 64 **3. Discussion (on the problem statement)**

65 The relevance of referring in the revised guideline to the following guidance documents need to be  
66 considered:

- 67 1. Guideline on good pharmacovigilance practices (GVP) Product- and Population- Specific  
68 Considerations Chapter P.III: Pregnant and breastfeeding women (EMA/653036/2019)<sup>3</sup>.
- 69 2. Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum III – Pregnancy  
70 prevention programme and other pregnancy-specific risk minimisation measures  
71 (EMA/608947/2021)<sup>4</sup>,
- 72 3. SWP recommendations on the duration of contraception following the end of treatment with a  
73 genotoxic drug (EMA/CHMP/SWP/74077/2020 corr. 3 in 2022)<sup>5</sup>,
- 74 4. ICH S5 (R3) Guideline on detection of reproductive and developmental toxicity for human  
75 pharmaceuticals<sup>6</sup> (2020), (substitute ICH S5A and S5B).
- 76 5. Non-Clinical Documentation for Mixed Marketing Authorisation Applications  
77 (CPMP/SWP/799/95)<sup>7</sup> should be considered and possibly deleted.
- 78 6. Non-Clinical Documentation for Herbal Medicinal Products in Applications for Marketing  
79 Authorisation (Bibliographical and Mixed Applications) and in Applications for Simplified  
80 Registration (EMA/HMPC/32116/05 Rev 1)<sup>8</sup>

#### 81 **Considerations to ensure alignment with the relevant guidelines and recommendations**

##### 82 **Key adverse pregnancy outcomes**

- 83 • Teratogenic effects include a range of embryo/fetal adverse outcomes in addition to congenital  
84 malformations, such as spontaneous abortion and fetal demise. These could be discussed further  
85 since in the current guideline congenital malformations are the only key marker of harm addressed  
86 in the risk assessment methodology and classification system.
- 87 • Second and third trimester effects. Consideration needs to be given to the possibility of adverse  
88 fetal effects arising from exposure *in-utero* beyond the first trimester since the current guideline  
89 recommends the assessment of malformative/teratogenic effects, based on the number of first  
90 trimester exposed pregnancies. Thus, the current guidance does not detail the possibility of

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<sup>3</sup> [Guideline on good pharmacovigilance practices \(GVP\) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding women \(europa.eu\)](#)

<sup>4</sup> [GVP Module XVI Addendum III - PPP \(europa.eu\)](#)

<sup>5</sup> [SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug \(europa.eu\)](#)

<sup>6</sup> [S5 \(R3\) Step 5 Toxicity to reproduction \(europa.eu\)](#)

<sup>7</sup> [Guideline on Non-Clinical Documentation for Mixed Marketing Authorisation Applications \(europa.eu\)](#)

<sup>8</sup> [Guideline on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products \(europa.eu\)](#)

91 exposure beyond first trimester of pregnancy. More expanded consideration of exposure windows to  
92 cover potential risks due to exposure during the entire pregnancy is required.

93 • Non-clinical considerations: Consideration needs to be given to the interpretation of animal/human  
94 exposure margins and the use of NAMs, according to ICHS5(R3). Reporting of animal data in SmPC  
95 section 4.6 can be nuanced in certain cases by using the ICHS5(R3) tiered system on how to  
96 interpret no observed adverse effect level (NOAEL) for embryo/fetal developmental toxicity testing  
97 and an exposure margin based endpoint (>25 fold) above which adverse developmental and  
98 reproductive toxicity (DART) findings are considered of minor concern for clinical use. Additionally,  
99 the use of NAMs as an alternative to animal testing under certain scenarios and possible weight of  
100 evidence building for products within a class of known developmental toxicants based on the  
101 pharmacological effect (e.g. anti-PD/L1), may in the near future provide additional human relevant non-  
102 clinical information not derived from animal studies. Also, non-clinical developments in assessing  
103 exposure via breast milk, and for assessing potential adverse outcomes, should be taken into  
104 account.

105 • Other topics:

106 ○ Long-term child outcomes following exposure during pregnancy, including  
107 neurodevelopmental disorders. Update guidance based on current experience.

108 ○ Vaccination of infants after *in-utero* exposure to immunomodulating or  
109 immunosuppressive medicines.

110 ○ Multigenerational effects.

111 ○ Embryo/fetal/child risks due to paternal exposure.

112 • Causality assessment of human reproductive adverse effects. Further description of key elements  
113 that may aid causality assessments of signals of reproductive adverse effects should be considered  
114 in updating the current guideline.

115 • Clinical study power. Sample size considerations needed to classify a product risk for congenital  
116 malformation should be reviewed, also considering alignment with the 2019 draft GVP guidance  
117 (EMA/653036/2019) regarding the definition of risk period and assessment of specific *versus* overall  
118 malformation rates.

119 • Susceptible exposure windows. More detailed information on susceptible periods of exposure should  
120 be added to the current guideline, as this is one important factor in assessing teratogenic risk.

## 121 **Breastfeeding**

122 Currently, there are new methods for estimating levels in breast milk and potential for adverse effects  
123 in a breastfed infant, more data leading to better understanding of the risk of medicines for infants  
124 exposed via breast milk. The guideline should be updated with current knowledge regarding risk  
125 assessment and reflect current views regarding how to communicate about risks in the SmPC and PL,  
126 including how to formulate recommendations.

## 127 **Male and Female Fertility**

128 Although information on risk assessment for male and female fertility is shortly described, there are no  
129 standard sentences being provided in the Guideline on the Summary of Product Characteristics<sup>9</sup>. It  
130 should be evaluated whether standard texts regarding fertility also should be developed, to cover all  
131 different aspects to be addressed in the SmPC section 4.6, and in the PL accordingly.

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<sup>9</sup> [Guideline on the Summary of Product Characteristics \(2005\). Rules governing Medicinal products in the European Community Volume 2A and 2B The Notice to Applicants](#)

## 132 **Standard texts**

133 The terminology of standard statements for use in section 4.6 “Fertility, pregnancy and lactation” of  
134 the SmPC, needs to be revised with an aim to improve the information to health care professionals and  
135 patients. Furthermore, development of corresponding standard texts for the PL is planned for.

## 136 **4. Recommendation**

137 The Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk  
138 Assessment Committee (PRAC) recommends the revision of the current “Guideline on risk assessment  
139 of medicinal products on human reproduction and lactation: from data to labelling” considering the  
140 issues identified above.

## 141 **5. Proposed timetable**

142 Released for consultation in May 2024, deadline for comments July 2024.

## 143 **6. Resource requirements for preparation**

144 The update of the guideline will involve members of the CHMP, PRAC, NcWP, 3RsWP, HCPWP, QRD,  
145 SmPC Advisory Group, EMA Labelling office and EMA pregnancy community. Drafting group meetings  
146 will be organised.

## 147 **7. Impact assessment (anticipated)**

148 The document is intended to provide updated guidance on the integration processes of clinical and  
149 non-clinical data for the assessment of the safety of medicines on fertility, in pregnancy and during  
150 breastfeeding.

151 The guideline will provide information on how to communicate potential or identified risks, specifically  
152 through the SmPC and PL. This will contribute to address specific information needs for healthcare  
153 professionals and patients planning pregnancy, being pregnant, or planning breastfeeding, to promote  
154 evidence based informed decisions and support management of diseases during pregnancy and  
155 breastfeeding. It will support a harmonised EU position and facilitate consistent recommendations  
156 within the pregnancy and breastfeeding related sections of the SmPC and PI during the life cycle of a  
157 medicinal product.

## 158 **8. Interested parties**

159 The pharmaceutical industry, European learned societies, and scientific organisations (e.g. Innovative  
160 Medicines Initiative (IMI), ConcePTION consortium), Academia, HCPs, and patients’ organisations.  
161 Consultation with other working parties or committees (e.g. CHMP, PRAC, NcWP, 3RsWP, QRD, HCPWP,  
162 PCWP) will be initiated as appropriate.

## 163 **9. References to literature, guidelines, etc.**

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