



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Good Pharmacovigilance Practices (EU-GVP)

## GVP PIII update after public consultation

---

Pharmacovigilance Platform Meeting  
30 October 2020

Corinne de Vries



## High level contents:

- Part A: scope, outlining the issues
- Part B: guidance to address the issues outlined in part A
- Part C: guidance that is specific to the EU

8	<b>Table of contents</b>	
9	<b>P.III.A. Introduction</b>	<b>3</b>
10	P.III.A.1. Pharmacovigilance aspects specific to the use of medicines in pregnant or breastfeeding women.....	4
11	P.III.A.1.1. Availability and interpretation of data.....	4
12	P.III.A.1.2. Adverse effects related to physiological changes of pregnancy.....	5
13	P.III.A.1.3. Susceptible periods and adverse pregnancy outcomes .....	5
14	P.III.A.1.4. Adverse effects in the child following exposure through breastfeeding .....	6
15	P.III.A.2. Terminology.....	6
16	<b>P.III.B. Structures and processes</b> .....	<b>8</b>
17	P.III.B.1. Risk management plan.....	8
18	P.III.B.2. Management and reporting of adverse reactions.....	9
19	P.III.B.3. Periodic safety update report.....	11
20	P.III.B.4. Post-authorisation safety studies .....	12
21	P.III.B.4.1. Pharmacokinetic studies on pregnancy-related physiological changes .....	13
22	P.III.B.4.2. Epidemiological studies.....	13
23	P.III.B.4.2.1. Pregnancy registries.....	14
24	P.III.B.4.2.2. Long-term pregnancy outcomes .....	15
25	P.III.B.4.2.3. Handling of bias and confounding.....	15
26	P.III.B.4.3. Clinical lactation studies .....	16
27	P.III.B.5. Signal management.....	17
28	P.III.B.6. Safety communication.....	17
29	P.III.B.7. Risk minimisation measures.....	18
30	P.III.B.7.1. Educational materials.....	19
31	P.III.B.7.2. Advice on effective contraception.....	20
32	P.III.B.7.3. Pregnancy prevention programme.....	20
33	<b>P.III.C. Operation of the EU network</b> .....	<b>21</b>
34	P.III.C.1. Submission of the PSUR in the EU.....	21
35	P.III.C.2. Post-authorisation safety studies in the EU.....	21
36	<b>P.III. Appendix 1: Questionnaire to collect information on pregnancy exposure</b> .....	<b>23</b>
37	<b>P.III. Appendix 2: Pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential</b> .....	<b>27</b>
38		
39		
40		



## Working principles we tried to adhere to:

- Encourage a 'step up' from current practice. More proactive data collection & evaluation of safety in this vulnerable population. 'If you don't ask, you don't get.'
- Order of contents in line with all other GVP
- No repetition of, or conflict with, guidance written elsewhere (e.g. requirements for PSUR, AE reporting, PASS, risk minimisation)
- If concerns are theoretical only, we do not issue guidance on those
- It is not our role to highlight benefits of breastfeeding
- Minimal use of examples



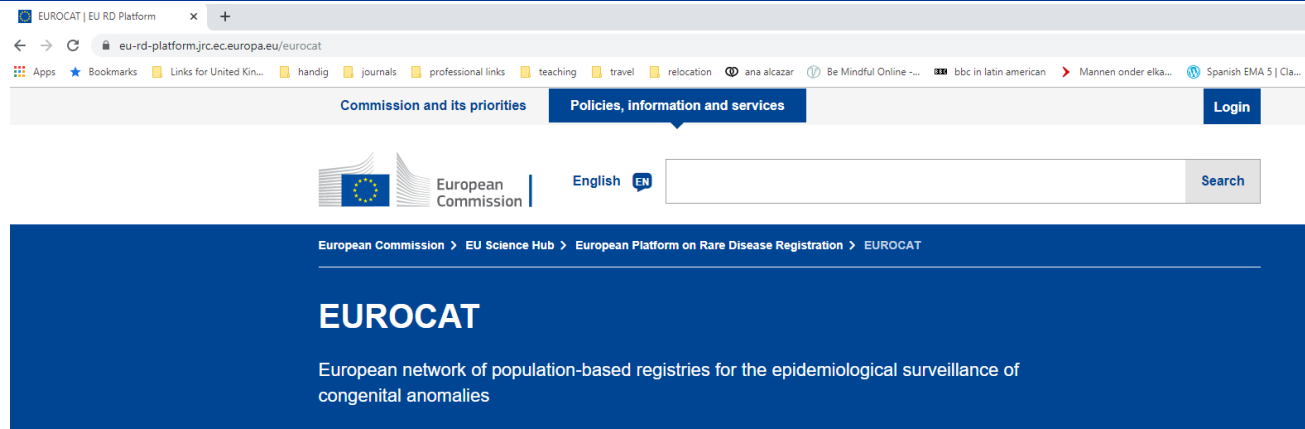
## Discussion items – part A

### Part A

- Terminology section - CHMP guideline or EUROCAT definitions?
- Possibility of harm by exposure through semen
- Need to 'state the obvious' given experience with MAH's submissions



# EUROCAT:



- Congenital malformations only
- Detected at any time – but the later the detection, the less likely to be reported
- Rates & data quality vary between centres
- Focus on outcomes; medicine exposure information is limited. Hence EUROmediCAT
- Focus on 'major malformations' – for reasons of pragmatism



## Discussion items – part B

- **PSURs**
  - sales data only or also age & sex specific utilisation data?
- **PASS**
  - When there is a **DUS**, ensure insight is obtained on confounders
  - Product specific **registries** vs hybrid study designs – everyone seems to agree on what is needed; the challenge is what can be required
  - Information on existence of registries in the PI & SmPC?
  - **Distinction between the implications of risk** in pregnancy & risk in breastfeeding



# Observation from our analysis of registries

- On the surface: reassuringly, no major teratogen found.
  - Scratch a little bit below the surface:
    - No protocol
    - No detailed data
    - Selective recruitment & eligibility, with  
as a result, low numbers & ??generalisability
- ➡ For all we know, there may still be a major teratogen here.



## Better use of existing methods & data sources

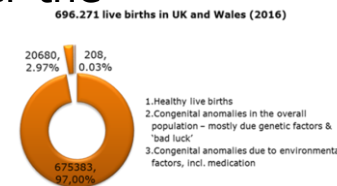
- Pre-authorisation: PK studies in breastfeeding
- Routine pharmacovigilance: PSURs, Eudravigilance
- Additional pharmacovigilance: hybrid approaches
- Translated into good risk minimisation measures
  - ✓ further developed in GVP XVI





## Please consider

- PSURs should provide age & sex specific utilisation data where available
  - Is there really no further information available? E.g. drug utilisation studies / safety studies that are not product-specific
- If there is a signal,
  - What, if any, is the impact of missing information e.g. on competing endpoints?
- No evidence of harm is not the same as evidence of no harm. Remember the numbers
- In terms of PASS, a lot more is possible today than 10 years ago
- Study requests & risk minimisation measures need to remain risk proportionate
- It is an emotive subject – with potentially impactful consequences. Careful consideration & good communication is crucial.





## Discussion items – part B

- **Risk minimisation**

- Avoiding pregnancy, avoiding exposure (pregnancy & breastfeeding) , risk mitigation when pregnancy unplanned
- Effective communication of risk & uncertainty (not 'lost' in large info packs, risk proportionate), empowering HCPs with information & skills
- Exposure through semen – theoretical only? Or solid evidence of risk?
- Effective contraception – how prescriptive do we want to be?
- Pregnancy prevention programmes (PPP) – at present, ***a lot of inconsistency*** between products.
  - To clarify the needs & achieve harmonisation. Driving factor: known teratogenicity in humans
  - Full PPP to have routine & additional RMMs. Most elements will be 'standard'; some decided on case-by-case basis
  - How the elements are to be implemented may depend on what is appropriate in each Member States (e.g. 'visual reminder' could be a pictogram or a text in colour on the pack)



# Thank you for your attention

---

**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Address for visits and deliveries** Refer to [www.ema.europa.eu/how-to-find-us](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

Follow us on  **@EMA\_News**