EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Sex and Gender in EU Regulatory Practice

Presented by Thorsten Vetter MD
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An agency of the European Union

EMA Analysis on gender bias in 2004

- All products, which received marketing authorisation in the EU between January 2000 and December 2003.
- Only pivotal trials included (main studies for the risk/benefit assessment)
- Additionally, random sample of 10 of the products to assess whether subgroup analyses by sex was conducted and safety data analysis.

Point estimates and CI were confronted with expected women proportion. While the conclusions were:

generally there seemed to be no or only negligible gender bias.

Exceptions appeared confirmed:
✓Under-representation of women in hypertension and diabetes trials
✓Overrepresentation of women in rheumatoid arthritis and allergy trials

Why do many studies show that women are underrepresented?

Possibly many of the cited studies are not registration trials. In these trials sometimes an easier enrolment is sought.

Women are more difficult to recruit and retain, e.g.:

- Economic issues
- Family/carer role

However, ***this is no reason to be complacent and ignore a scientific and societal gap***.

Therefore, must avoid assumptions: ensure we have sufficient evidence; particularly for early studies including PK/PD (*Phase I/II is mostly male*).

Improving the evidence base

Clinical Trial Regulation (EU) No 536/2014

Art 6 (Assessment report of CTAA):

the relevance of the clinical trial, including ***whether the groups of subjects participating in the clinical trial represent the population to be treated****, or if not, the explanation and justification provided in accordance with point (y) of paragraph 17 of Annex I to this Regulation*

Art 10 (specific considerations for vulnerable populations):

If according to the protocol a clinical trial provides for the participation of specific groups or subgroups of subjects, where appropriate, specific consideration shall be given to the assessment of the application for authorisation of that clinical trial ***on the basis of expertise in the population represented*** *by the subjects concerned*

Clinical Trial Regulation (EU) No 536/2014

Annex I (application dossier for the initial application):

PROTOCOL: shall include at least

(*y) a justification for the gender and age allocation of subjects and, **if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria**;*

Annex V (Summary of results for Laypersons):

*4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and **gender breakdown**; inclusion and exclu sion criteria);*

Role of subgroup analysis

*Definition: Any evaluation of treatment effects for a specific end point in subgroups of patients defined by baseline characteristics. The end point may be a measure of treatment efficacy or safety.**

EMA workshop on the investigation of subgroups in confirmatory clinical trials 07 November 2014

❑ Guideline on the investigation of subgroups in confirmatory clinical trials (public consultation ended July 2014)

* R Wang et al. N Engl J Med 2007; 357:2189-2194

Reasons for doing subgroup analyses

- Obtain information about patients where, based on their baseline characteristics, it is plausible that the efficacy or safety could be different when compared to the overall population
- Explore the influence of baseline characteristics – even the ones which would be thought not to influence efficacy and safety of the medicine
- *Save a failed trial*
- *Obtain pseudospecific claims in the label*
- *Reach a compromise on a population where the benefit-risk balance could be positive*

Subgroups

- **Sex**
- Age
- Race
- Geographical region
- Disease severity
- Reduced elimination capacity
- Concomitant medication
- Previous treatment

Conclusion on subgroup analyses

- Generally, the number of potential subgroup analyses is increasing generating multiplicity issues
- In pivotal trials, the analyses should be limited to subgroups where it is clinically or biologically plausible that the efficacy or safety of a medicine could be different
- *For recruitment to trials there should be sufficient numbers so that subgroup analyses are valid with robust findings that can be applied in practice*
- *Informative, Phase I/II studies (e.g. including an adequate gender representation) can allow to pre-specify and fully power relevant subgroups: then more precise estimates of efficacy and safety can be derived*

CHMP Assessment Report Template

Baseline characteristics

Baseline demographic and clinical characteristics of each group. Describe particularly any asymmetry in characteristics across treatment arms.

- *Discuss how study population reflects intended indication (or defer to overall conclusions).*
- *Discuss similarities and any discrepancies between treatment arms (if applicable).*
- *Discuss treatment compliance, if appropriate.*

Special populations

Exploratory analysis of data across studies that may contribute to the understanding of variations in drug pharmacokinetics and possible statements on the consequences may be displayed here. ***These variations may be related to extrinsic or intrinsic factors such as age, gender****, race, smoking status, metabolic polymorphism, renal function and hepatic insufficiency*

CHMP assessment report template:

A **tabular overview of the relevant clinical studies**; study number, design and number of patients in treatment arms, baseline characteristics such as age, gender and severity of disease, efficacy parameters and efficacy results should be included. Example table for study details:

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint

3.6. Analysis performed across trials (pooled analyses AND meta-analysis)

Criteria used for these analyses should be stated and may involve exploratory analysis on the whole database considering different **effect modifiers (gender**, age, drug-disease interactions, smoking etc.). In addition dose-effect relationship in special

4.6. Safety in special populations

Short summary of all available information both derived from preclinical and clinical studies in order to substantiate the specific statements in the SPC (e.g. **gender related differences**, risks for the use in pregnant women, breast feeding, potential effects on fertility, etc).

Product information

The **SmPC** is the basis for information for healthcare professionals on how to use the medicinal product safely and effectively, including in special populations, such as children, older people and pregnant women.

- Differences in PK or efficacy should be mentioned as appropriate.

- In accordance with the SmPC guideline, efforts should be made by the Marketing Authorisation Applicant or Holder to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential (section 4.6).

- All available knowledge should be taken into account, including clinical studies and post-marketing surveillance, pharmacological activity, results from non-clinical studies, and knowledge about compounds within the same class.

SmPC guideline:http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

How can we get better data?

- Ensure adequate Phase I/II studies
- Increase attention to unjustified exclusion criteria in pivotal clinical studies
- Analyse all data available and provide relevant and transparent information
- EMA participation in regulatory science projects (e.g. IMI projects like PROTECT) to develop new methodologies for data collection throughout life cycle
- Use of new European Pharmacovigilance legislation and new legislation on post-authorisation efficacy studies (PAES)

Post-authorisation efficacy studies (PAES): not a new concept

Prior to Delegated Regulation (EU) 357/2014 separate legal frameworks existed for PAES in the context of

- Conditional Marketing Authorisation (MA)
- MA in exceptional circumstances
- MA for ATMPs
- The paediatric use of a medicinal product
- Referral procedures

PAES (Delegated Regulation (EU) 357/2014)

May be required for centrally or nationally authorised products either:

- **At the time of granting the marketing authorisation**: concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed
- **After granting the marketing authorisation**: the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly
- *General guidance on PAES is currently being drafted*

Concept paper on GVP: safety in pregnancy and lactation

Under Development

• aiming at defining standards for post-marketing measures to collect meaningful safety information on medicine use in pregnancy and lactation which is not feasible before licensure

• targeting information from products which have been on the market for longer as these products are used during pregnancy and lactation, in particular OTC products

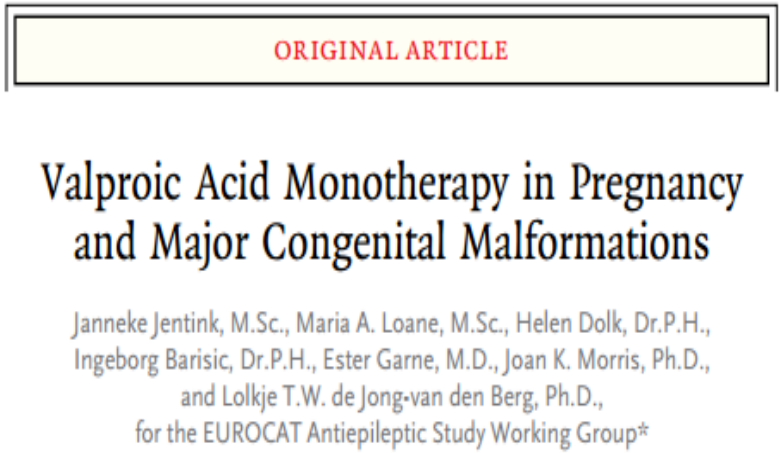
•women of childbearing potential, not only pregnant women in focus: 20-50% of pregnancies are unplanned

•optimised use of appropriate pharmacovigilance measures: RMP, routine signal detection activities, pregnancy registries, PASS, risk minimisation measures, PSUR requirements

•Publication envisaged for mid 2016

EUROmediCAT: FP7 project 2011-2015

- EUROCAT: European network of population-based registries for the epidemiologic surveillance of congenital anomalies
- Linkage of electronic health with EUROCAT data
- Internet use and drug safety
- Literature reviews for products covered
- Utilisation studies; countries: Denmark, Netherlands, UK / Wales, Italy, Norway)
- Case-malformed control studies
- Specific topics: Asthma medications, Epilepsy medications, SSRIs, Diabetes medications



ORIGINAL ARTICLE

Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations

Janneke Jentink, M.Sc., Maria A. Loane, M.Sc., Helen Dolk, Dr.P.H., Ingeborg Barisic, Dr.P.H., Ester Garne, M.D., Joan K. Morris, Ph.D., and Lolkje T.W. de Jong-van den Berg, Ph.D., for the EUROCAT Antiepileptic Study Working Group*

EUROmediCAT conclusions

http://euromedicat.eu/content/Final%20Publishable%20Executive%20Summary%20April%202015.pdf

- Pregnant women are excluded from RCTs to protect the foetus
- Once on the market, drug use in pregnancy occurs
  - 3.3% (Italy) -9.6% (Wales) of pregnancies exposed to SSRIs
  - 3.4% (Norway) – 9.4% (UK) of pregnancies exposed to asthma medicines
- It is easy to purchase isotretinoin from e-pharmacies via the internet without a prescription. advice regarding safety in pregnancy, adequate warnings are not always in place here.

Insulin analogues

- Lower risk of major CAs in births exposed to only insulin analogues (3.8%) during the first trimester significantly lower than in only human insulin – mostly CHD

  (8.6%); RR = 0.42 (95% CI: 0.24-0.73)

- Still birth and spontaneous abortion (4.0%) higher among only insulin analogue group compared to only human insulin group (1.4%)

'Conclusions from the study: This study shows that first trimester exposure to insulin analogues did not increase the risk of congenital anomalies compared to exposure to human insulin. The decrease risk of CHDs among the insulin analogues exposed provides a further piece of evidence of the safety of insulin analogues with regards to CA. The higher risk of foetal death in relation to insulin analogues warrants further investigation.'

EUROmediCAT recommendations

- ***Risk of disease may be more severe than risk of treatment***. Better information needs to be made available to help inform choice
- Scarcity of information on medicine safety in pregnancy is intolerable and must be remedied by investment in research and pharmacovigilance.
- MA licenses of new medicines should be revoked if post authorisation monitoring insufficient
- Data protection regulations in Europe should allow the sharing of information across borders for pharmacovigilance, including pooled databases.

PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PROTECT

Methods for Pharmacoepidemiological studies
Signal detection

PROTECT WP4 – New methods for data collection from consumers: study in pregnant women.

This study showed that new ways of collecting information on lifestyle factors, health and use of medicines throughout pregnancy in a large number of pregnant women via telephone and internet is feasible and informative.

http://www.imi-protect.eu/pregnancyStudy.shtml

Number of different medicinal products taken during pregnancy*

No. of Medicinal Products Taken	DK % (n)	NL % (n)	PL % (n)	UK % (n)	**Total % (n)**
None	18% (117)	21% (98)	24% (59)	13% (90)	**18% (364)**
1	16% (102)	23% (109)	22% (54)	17% (119)	**19% (384)**
2	17% (108)	17% (81)	15% (37)	16% (113)	**16% (339)**
3	14% (90)	16% (74)	12% (28)	15% (108)	**15% (300)**
4	11% (73)	8% (37)	8% (19)	10% (74)	**10% (203)**
≥ 5	23% (149)	16% (77)	18% (44)	29% (205)	**23% (475)**

* Excluding iron, folate and multi-vitamins

Conclusion

- It is possible to recruit women early in pregnancy before they may have consulted HCPs
- Direct to consumer studies offer important benefits in collecting certain data not found in EHR
- Will be most informative when combined with selected data from other sources to validate clinical outcomes of interest, and to corroborate most important exposures

Examples for recent benefit risk reviews:

PRAC recommends strengthening the restrictions on the use of valproate in women and girls

Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation

d use of bromocriptine for duction

Press release

22/11/2013

Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation

Product information to be updated to help women make informed decisions about their choice of contraception

The European Medicines Agency has now completed its review of combined hormonal contraceptives (CHCs), particularly of the risk of venous thromboembolism (VTE or blood clots in veins) associated with their use. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of VTE with all CHCs is small.

The review has reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.

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medical reasons for stopping lactation, such

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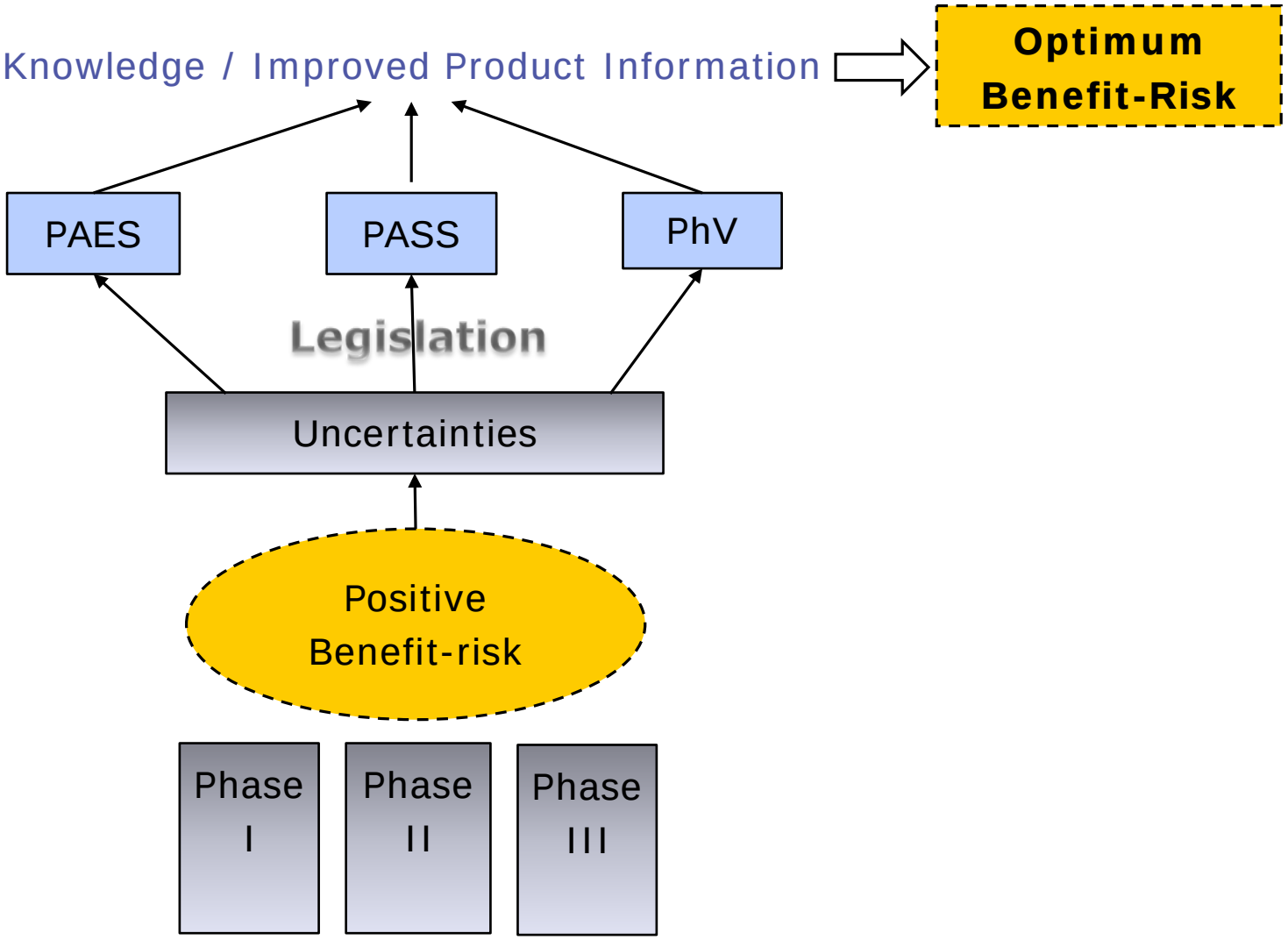
n, who should not breastfeed.

Key messages

- The importance of representation of both genders in clinical trials is acknowledged.
- It may not be that **representation** is equal but **needs to be scientifically meaningful**; ideally subgroup analyses should be adequately powered to allow for meaningful conclusions that can be reflected in the product information.
- The **new Clinical Trials Regulation** is a major step forward in improving the evidence-base on which a medicine is approved for different population groups, such as women and making clinical trial date more transparent.
- In addition, the new PhV legislation and the 2014 Delegated Regulation on PAES provide a firm legal basis to collect new and additional evidence.
- Additional GVP guidance to further specify pharmacovigilance measures to improve available safety evidence, e.g. in women of childbearing age and lactation
- All this leads to improved knowledge which should be reflected in the product information to ensure safe and effective use.

Gender through the product life cycle



Thank you for your attention

Further information

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