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Do gender-specific data from early-phase clinical trials translate into therapeutic recommendations?

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Overview

- General guidance regarding women in drug trials
- 2012 Canadian draft guidance on women in clinical trials and analysis of data by sex
- Gender representation in EMA pivotal studies
- Gender-specific data in EMA SmPCs
- Conclusion

Guidance regarding women in drug trials

- 1993 FDA
  „Guideline on Gender Differences in the Evaluation of Drugs"
- 2004 Germany
  „12. AMG Novelle"
- 2005 ICH
  „Guideline Gender Considerations in the Conduct of Clinical Trials"
- 2012 Canadian Draft Guidance „Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex"

Guidance regarding women in drug trials

- ICH E8 (General considerations)
- ICH E2 (Safety)
- ICH E4 (Dose-response)
- ICH E3 (Study reports)
- ICH E14 (thorough QT)
- ICH M3R2 (Non-clinical safety)
- ICH Guidelines M4E (CTD efficacy)
- Bioequivalence 2010

2005 ICH Gender Considerations
(EMEA/CHMP/3916/2005-ICH)

- „Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug“

German Medicines Act (AMG, §42)

- Guidance for Competent Authority / Ethic Committee Approval („GCP-V“) should include
  - ... Description of procedures on adequate participation of women and men in clinical trials

    („Angaben zur angemessenen Beteiligung von Frauen und Männern als Prüfungsteilnehmerinnen und Prüfungsteilnehmer“)

German Medicines Act (AMG, §42)

- Competent Authority / Ethic Committee Approval may be withheld in case
  - ... trial does not comply with the current state of the (scientific) art
  - ... trial is not suited to prove efficacy and tolerability including the differing modes of action in women and men

    („die klin. Prüfung ungeeignet ist, den Nachweis von Unbedenklichkeit und Wirksamkeit des Arzneimittels einschließlich einer unterschiedlichen Wirkungsweise bei Frauen und Männern zu erbringen“)

Canadian Draft Guidance 2012

- Dose-finding, pharmacokinetic and pharmacodynamic studies should include both men and women to identify potential sex-related differences in drug metabolism, … differences in dose-response, and/or safety
- Consider ICH M3R2 Guidance on timing for inclusion of women of child-bearing potential
- Consider pregnancy prevention measures (Appendix to Guidance)

Canadian Draft Guidance 2012

- If data from early studies suggest potential clinically significant sex-related differences, consider hypothesis testing in subsequent trials and determine if sex differences are meaningful and clinically relevant
- If data from early phase trials do not indicate potential sex-related differences, it cannot be assumed that clinically relevant differences do not exist; …carry out post hoc analysis of the data by sex in Phase III trials

Canadian Draft Guidance 2012

- … If possible differences by sex are identified in post hoc analyses, plan further study prior to marketing, or monitoring post-market

- Use post-market data collection where confirmatory trials generate signals or hypotheses about potential sex-related differences

Canadian Draft Guidance 2012

- In the context of a drug submission, … carry out and present an analysis … on the influence of sex, where data indicate that sex differences are a consideration, or where the product belongs to a class where sex differences are known.
- This analysis should be carried out for individual studies, as well as in the integrated analysis of efficacy and safety.
- In case of sex-related differences … confirm the reasons for these differences (e.g. whether they are related to organ size/weight, physiological differences, or potential route of administration, dose, dosing regimen, dosage form or product formulation)

Canadian Draft Guidance 2012

- Determine how to mitigate the effect of sex-related differences in the clinical setting
- Relevant findings with respect to sex differences in response to therapeutic products should be reflected in the product information

Review of EMA Pivotal Trials (2000-2003)

- 240 pivotal trials including 84 products were reviewed for adequate representation of true patient population and women in particular
- No, or clinically negligible, evidence for gender bias
- Women were underrepresented in hypertension, diabetes and hepatitis B trials
- Women were overrepresented in trials on rheumatoid arthritis and allergic conjunctivitis
- Gender bias was no serious problem in trials submitted for marketing authorisation

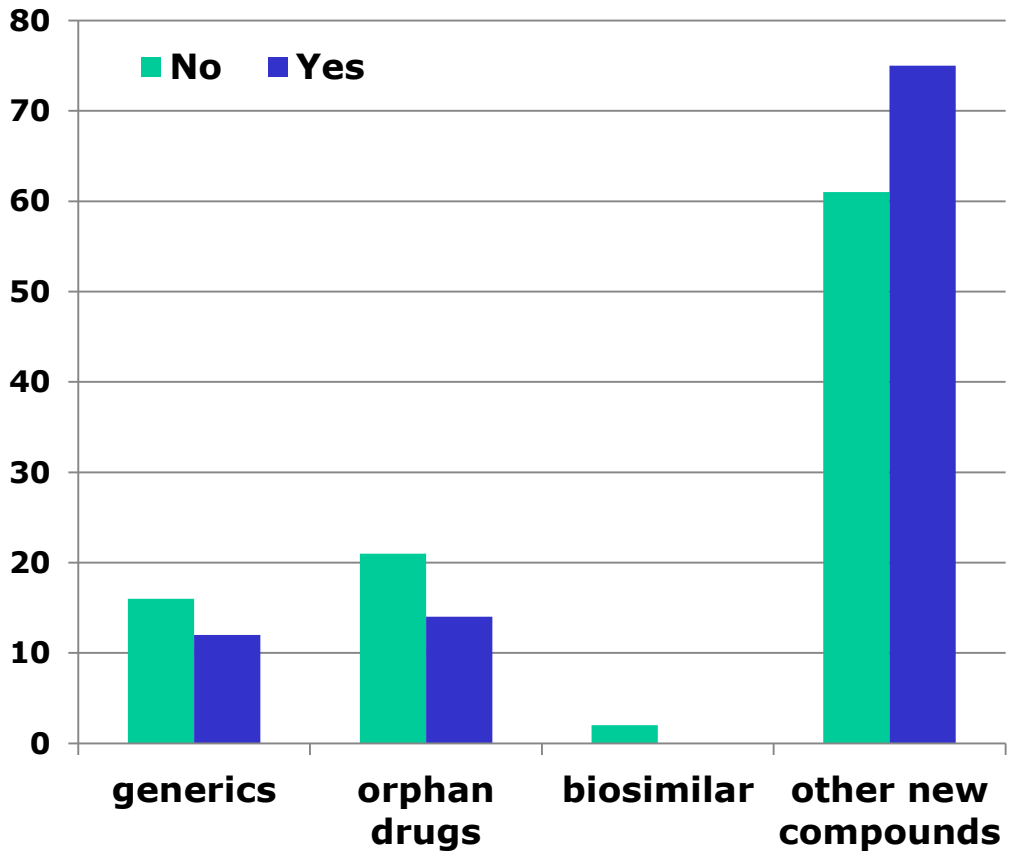
Müllner M et al. Int J Clin Pharmacol Ther 2007;45(9):477-84

Review of EMA SmPCs (2007-2012)

- EMA human medicines website
- 356 products granted marketing authorisation between 4 January 2007 and 31 January 2012
- Screened for gender-specific information
- Exclusion of gender-specific indications, like female/male hormonal treatment, prostate cancer, postmenopausal osteoporosis, erectile dysfunction
- Generics with different brand names, only 1-2 with most recent date of authorisation included
- 198 SmPCs (Summary of Medicinal Product Characteristics) were reviewed

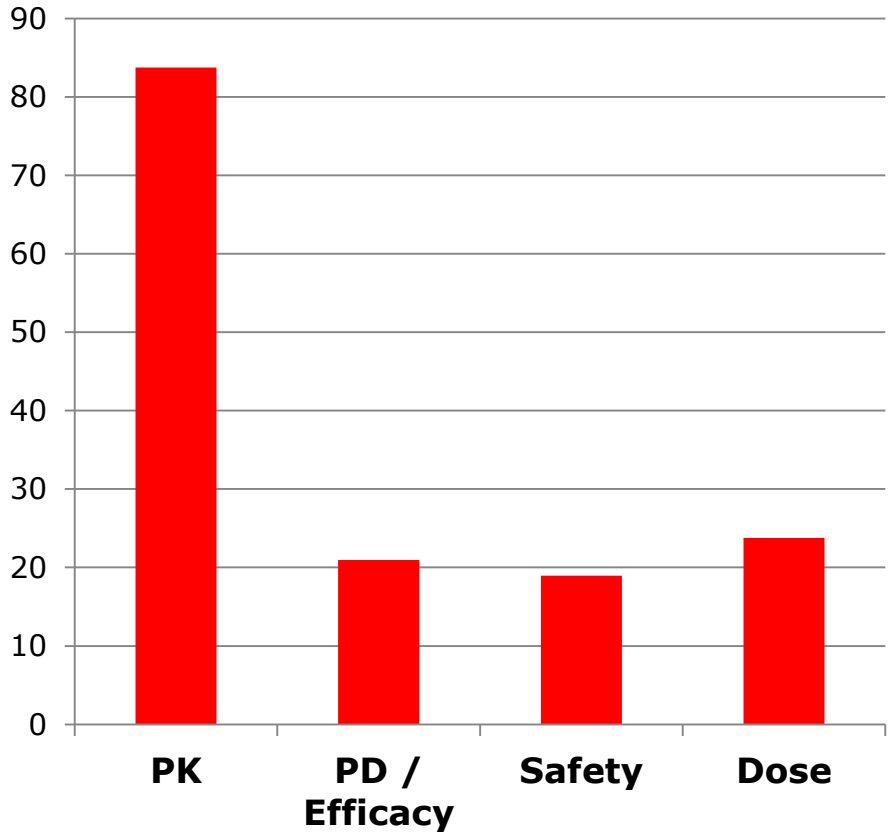
Gender-specific data in EMA SmPCs

- Gender-specific information provided in 101/198 newly approved products (51%)
- Not given in 97/198 newly approved products (49%)



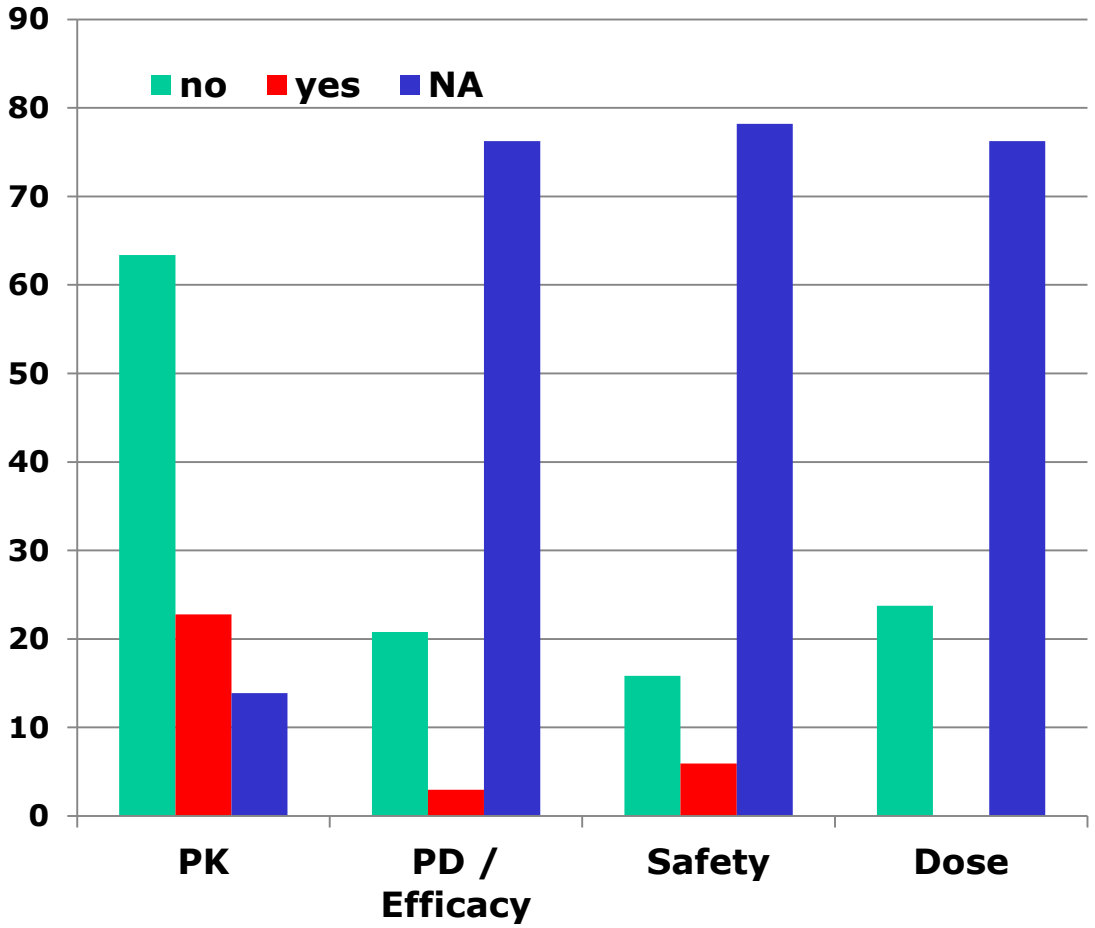
Gender-specific information provided on

- Pharmacokinetics (84%)
- Pharmacodynamics / Efficacy (21%)
- Safety (19%)
- Dose recommendation (24%)



Differences in gender - „yes" / „no"

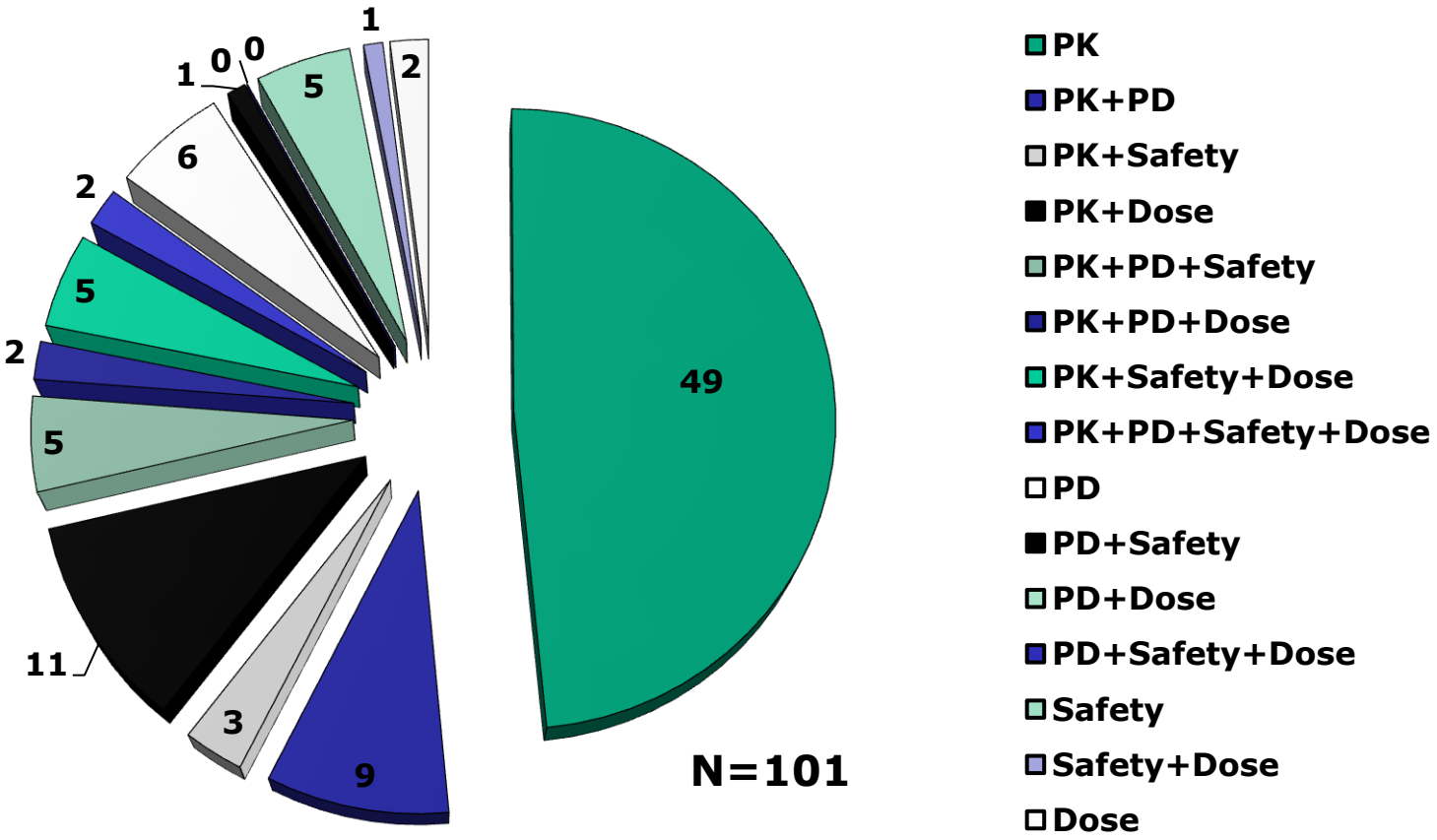
- Gender differences in PK were observed in 22.8% of compounds approved by EMA between 2007 and 2012
- … in PD in 3% of compounds
- … in safety in 6% of compounds
- … no changes in dose recommendations



Gender differences in Pharmacokinetics

- 23/101 compounds with differences in PK between male and female subjects
- 22 with higher exposure in women, 1 with lower exposure
- 11 compounds with gender-differences in PK refer to dose recommendations
- No changes in dose are advised, reasons are provided for 3 compounds only (no changes in safety)
- 12 compounds with gender-differences in PK do not provide any information on dose

Content of gender-specific information



Information – sufficient to be useful?

- **Active substance exposure was about 40 % to 50 % higher in female patients**
- **There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women**
- **Given the available clinical and kinetic data, no dose adjustment is necessary**

- New compound for oral anticoagulation

Information – sufficient to be useful?

- **The starting dose and dose range need not be routinely altered for female patients relative to male patients. When more than one factor is present which might result in slower metabolism (…), consideration should be given to decreasing the starting dose. Dose escalation, should be conservative in such patients**
- **In female versus male subjects the mean elimination half life was somewhat prolonged and clearance was reduced**
- **The magnitude of the impact of … gender, or … on clearance and half-life is small in comparison to the overall variability between individuals**
- **A comparable safety profile in female (n=467) as in male patients (n=869) was observed**

- Oral treatment for schizophrenia

Information – sufficient to be useful?

- **Complete response to the antiemetic regimen was reached in 209/324 (65 %) of women and in 83/101 (82 %) of men**
- **Pharmacokinetics have not been evaluated in special populations**
- **No clinically relevant differences in pharmacokinetics are expected due to gender**
- **No dose adjustment is necessary based on gender**

- Prevention of chemotherapy-induced / post-operative nausea and vomiting

Information – sufficient to be useful?

- **Female gender at the initiation of therapy is associated with a greater risk of hepatic adverse events**
- **Female patients showed a 13.8 % lower clearance than did male patients POP PK)**
- **No dose recommendation given**

- Compound for HIV treatment

Conclusions

- Competent Authorities demand gender-specific data for marketing authorisation
- About 50% of SmPCs for compounds granted EMA marketing authorisation between 2007 and 2012 provide gender-specific information
- This information mostly refers to PK (in about 80% of compounds with gender-specific data)
- PD/efficacy and safety data are provided only in about 20% of compounds with gender-specific data
- None of the gender-specific information translated into dose recommendations
- Gender-specific information lacks structure