Inclusion of Women in Clinical Trials, a regulator's perspective

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Drugs & Gender in Society

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‹ Actueel

6 VRAGEN OVER VROUWEN EN GENEESMIDDELEN

18 mei 2016

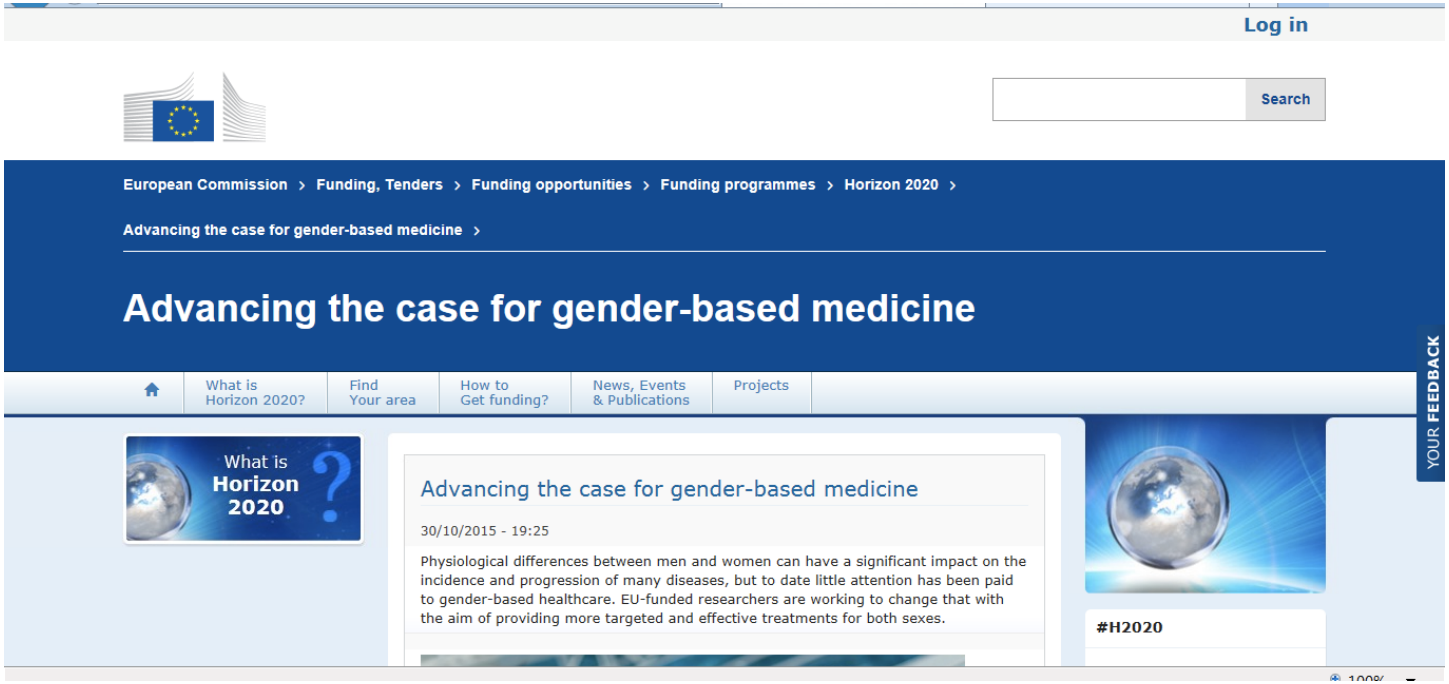
Wat zijn de feiten als het gaat om sekseverschillen bij geneesmiddelenonderzoek- en gebruik? Is het echt waar dat vrouwen meer medicijnen slikken dan mannen en er te weinig onderzoek wordt gedaan op vrouwen? WOMEN Inc. pleit samen met de Alliantie Gender en Gezondheid voor zorg op maat waar de gezondheidsverschillen tussen mannen en vrouwen worden meegenomen. Ook bij geneesmiddelen blijft dit een belangrijk onderwerp. In dit artikel zetten wij een aantal vragen en antwoorden over m/v verschillen bij medicijngebruik op een rijtje.

1. Wat zijn verschillen tussen mannen en vrouwen in bijwerkingen?

- Vrouwen hebben 60% meer kans op bijwerkingen van medicijnen.

Drugs & Gender in Public Funding

Drugs & Gender in Public Funding



Drugs & Gender in Scientific Publications

GENDER MEDICINE/VOL. 7, NO. 4, 2010

Commentary

Sex, Gender, and Pharmaceutical Politics: From Drug Development to Marketing

Jill A. Fisher, PhD[1]; and Lorna M. Ronald, PhD[2]

[1]Center for Biomedical Ethics & Society, Vanderbilt University, Nashville, Tennessee; and [2]Interdisciplinary Studies Program, John Jay College (City University of New York), New York, New York

Conclusions: Sex and gender play important roles in pharmaceutical regulation, from the design of clinical trials and the approval of new drugs to advertising and postmarketing surveillance. However, regulatory agencies pay insufficient attention to both biological sex differences and sociocultural gender norms. This disregard perpetuates inequalities by ignoring drug safety problems that predominate in women and by allowing misleading drug marketing that reinforces gender stereotypes. Recommendations have been made to improve the regulation of pharmaceuticals in regard to sex and gender. (*Gend Med.* 2010;7:357–370) © 2010 Excerpta Medica Inc.

Drugs & Gender Agenda MEB (2017)

College ter Beoordeling van Geneesmiddelen

Home > Voor mensen > Zorgverleners >

Man-vrouw verschillen en geneesmiddelen

Voordat geneesmiddelen op de markt komen, onderzoeken de fabrikanten de werking hiervan bij de patiëntengroep waarvoor het middel is bedoeld. Als geneesmiddelen in Nederland bijvoorbeeld ook aan vrouwen worden voorgeschreven, dan moeten deze ook bij hen zijn onderzocht. Het CBG laat alleen geneesmiddelen toe als deze voldoende zijn onderzocht en als deze goed genoeg werken en de bijwerkingen acceptabel zijn.

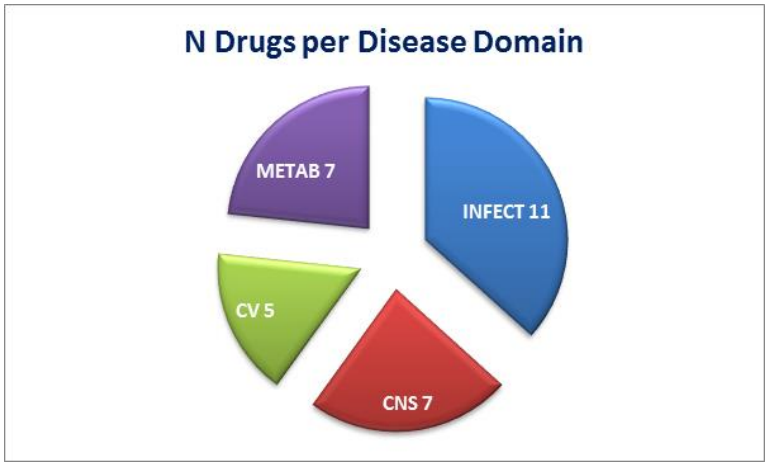
De biologische verschillen tussen mannen en vrouwen zijn belangrijk voor de diagnose, behandeling, het verloop van verschillende ziekten en medische condities. Daarom besteedt het CBG bij de beoordeling en bewaking van geneesmiddelen onder meer aandacht aan de verschillen en overeenkomsten tussen mannen en vrouwen. Het CBG slaat deze kennis en gegevens over geneesmiddelen op in de registratiedossiers van geneesmiddelen.

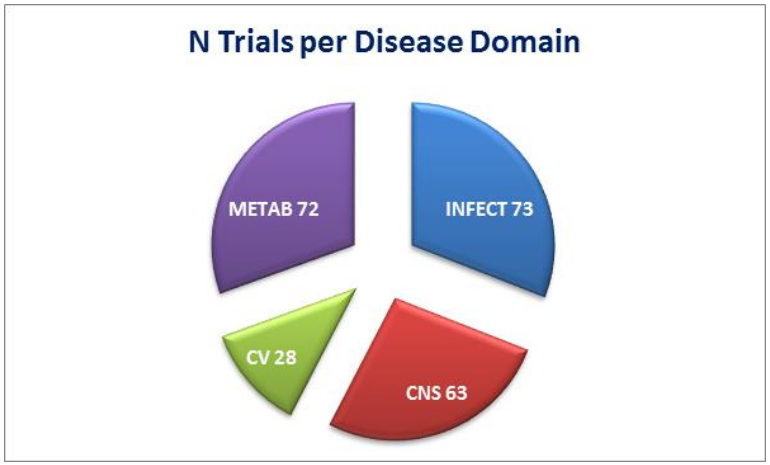
Drugs & Gender Agenda MEB

3 small scale regulatory science projects

- External validity of B/R decisions?
  - A cross-sectional survey of drug dossiers and phase 3 clinical trials
    - Infectious Disease
    - Central Nervous System
    - Cardiovascular
    - Metabolic
  - Central procedures 2011-2015
  - Source material: EPAR/SmPC & MEB database
- Recommendations for Industry
  - Attention for gender in clinical guidelines
- Gender specific PK/PD in the label (e.g. dosing)
  - A cross-sectional survey of drug dossiers and phase 1 clinical studies

Disease Domains (4), Drugs (30), Trials (236) & Patients (152.792)





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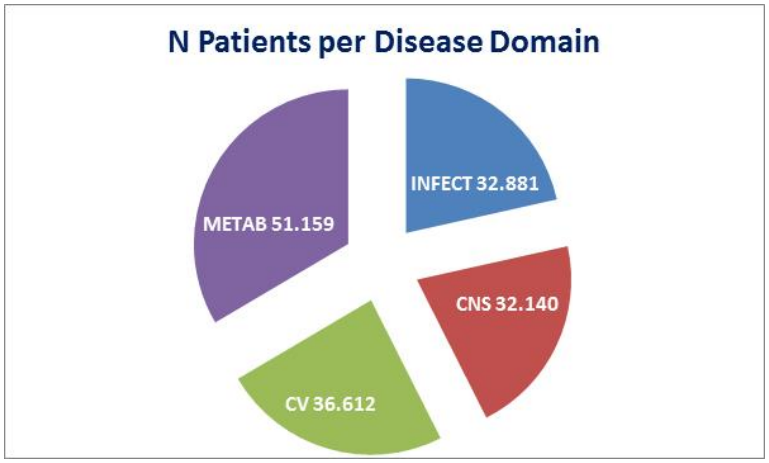
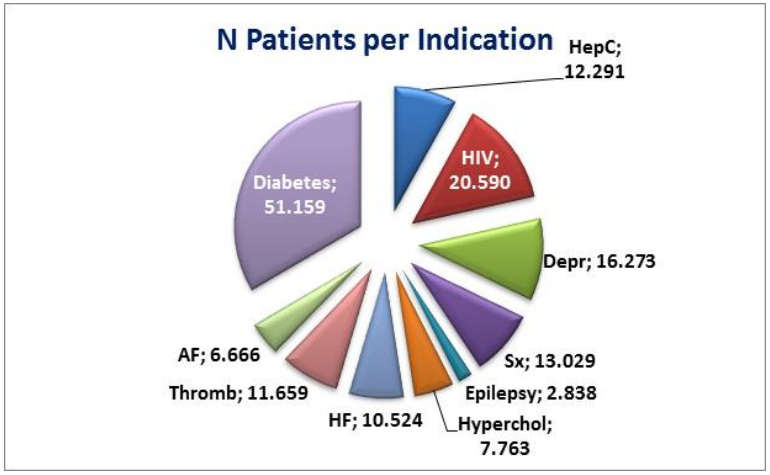
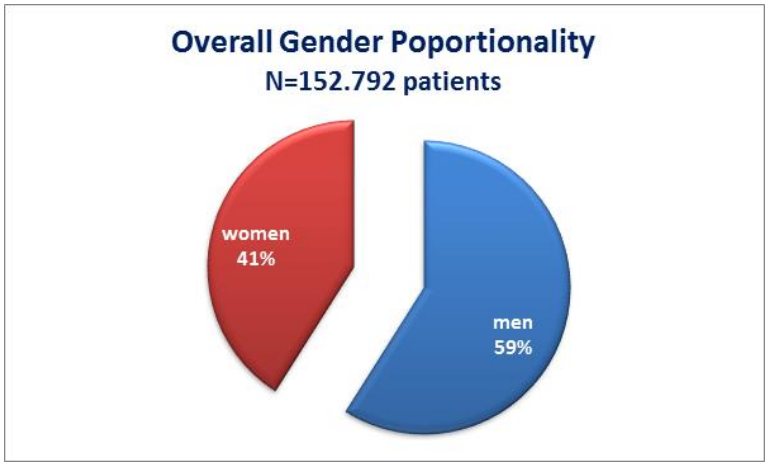
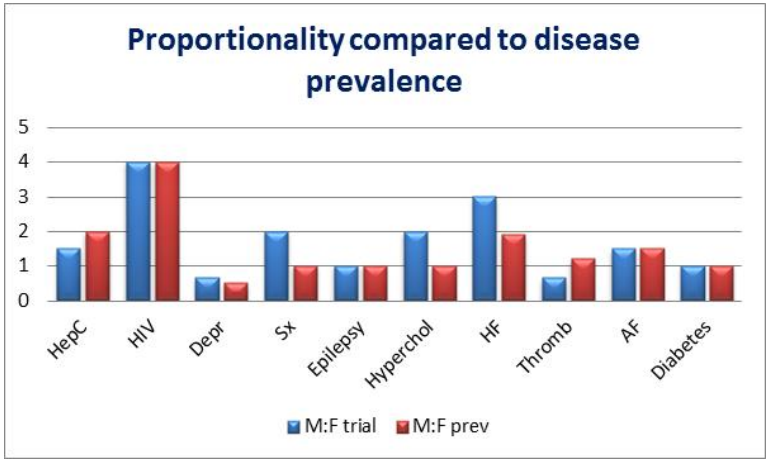




Inclusion of women in phase 3 Clinical Trials





Conclusion

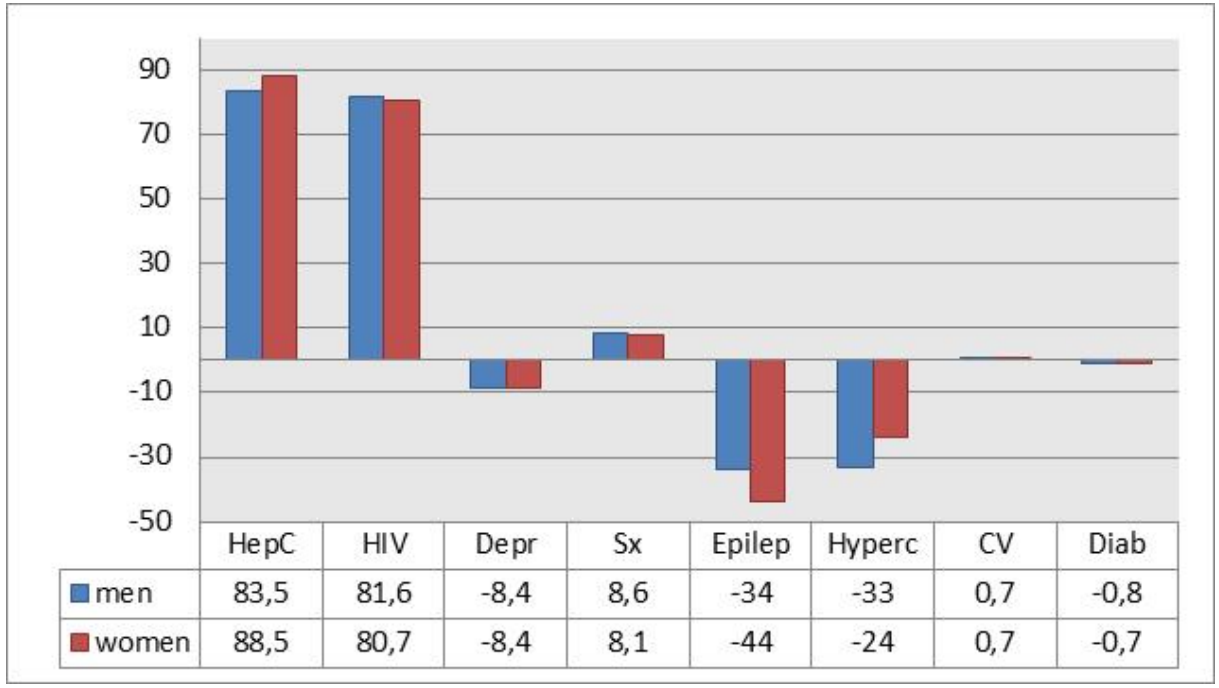
- Women are included in phase 3 clinical trials: external validity of trial data is safeguarded for licensing purposes.

- Gender disproportionality is **two sided**: skewed towards men in the cardiovascular domain and schizophrenia, skewed towards women in hepatitis C and thrombosis:

Effect size by Gender

Indication	Trial Objective
HepC	% subj with SVR
HIV	% subj with HIV-1 RNA<50 copies/ml
Depr	change from baseline HAM-D or MADRS
Sx	relapse rate as HR
Epilepsy	% change from baseline in seizure frequency
Hyperchol	change from baseline in LDL
HF	HR/RR to CV hosp or death
Thromb	HR/RR to CV hosp or death
AF	HR/RR to CV hosp or death
Diabetes	change from aseline HbA1c

Effect size by Gender



	HepC	HIV	Depr	Sx	Epilep	Hyperc	CV	Diab
men	83,5	81,6	-8,4	8,6	-34	-33	0,7	-0,8
women	88,5	80,7	-8,4	8,1	-44	-24	0,7	-0,7

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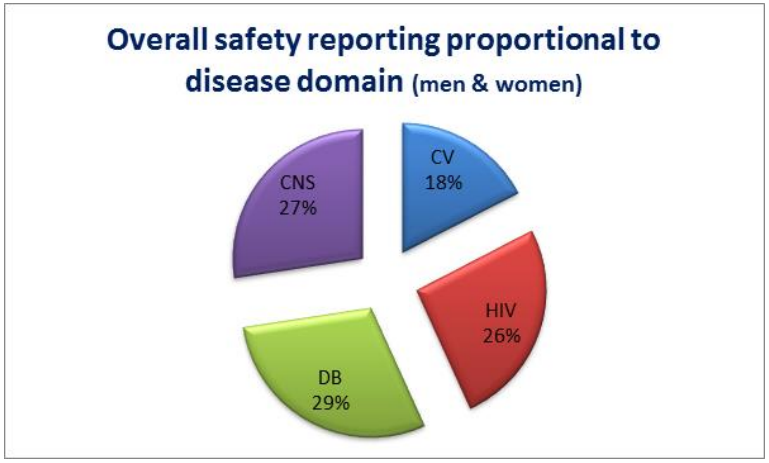
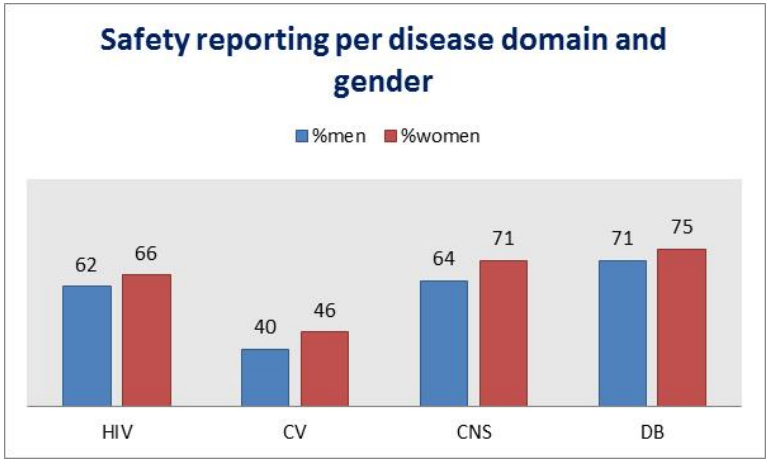
Safety reporting





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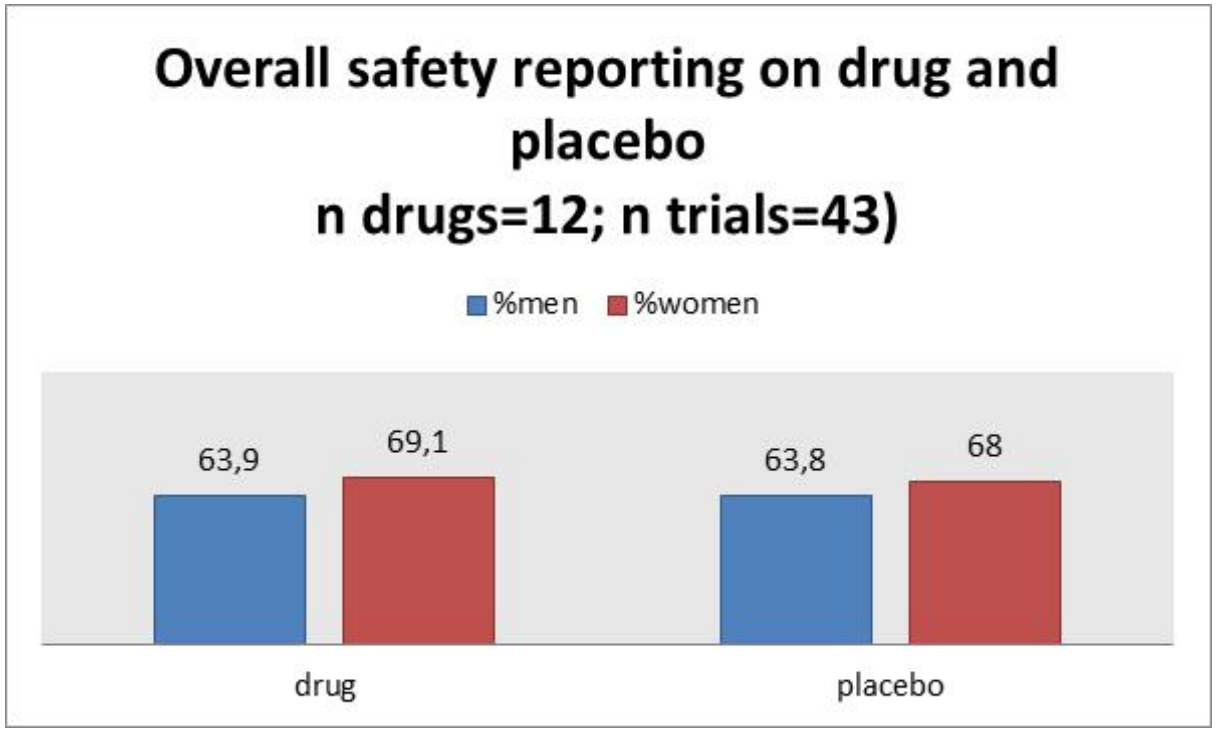

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- Safety reporting is gender sensitive: the proportion women reporting on safety is higher and consistent on drug and placebo

Recommendations for Industry

Guideline	Year	Gender	Cinical	Pharmacol
HepC	2009	no		
Diabetes	2012	yes	study population	
Depr	2013	no		
Sx	2013	yes	study population	
AF	2014	yes	study population	
HF	2015	yes	outcome/cardiac events	
HIV	2017	yes	treatment naïve pts	PK/PD
Hyperchol	2017	yes	study population	PK/PD
Thromb	2017	yes	study population/statistics	

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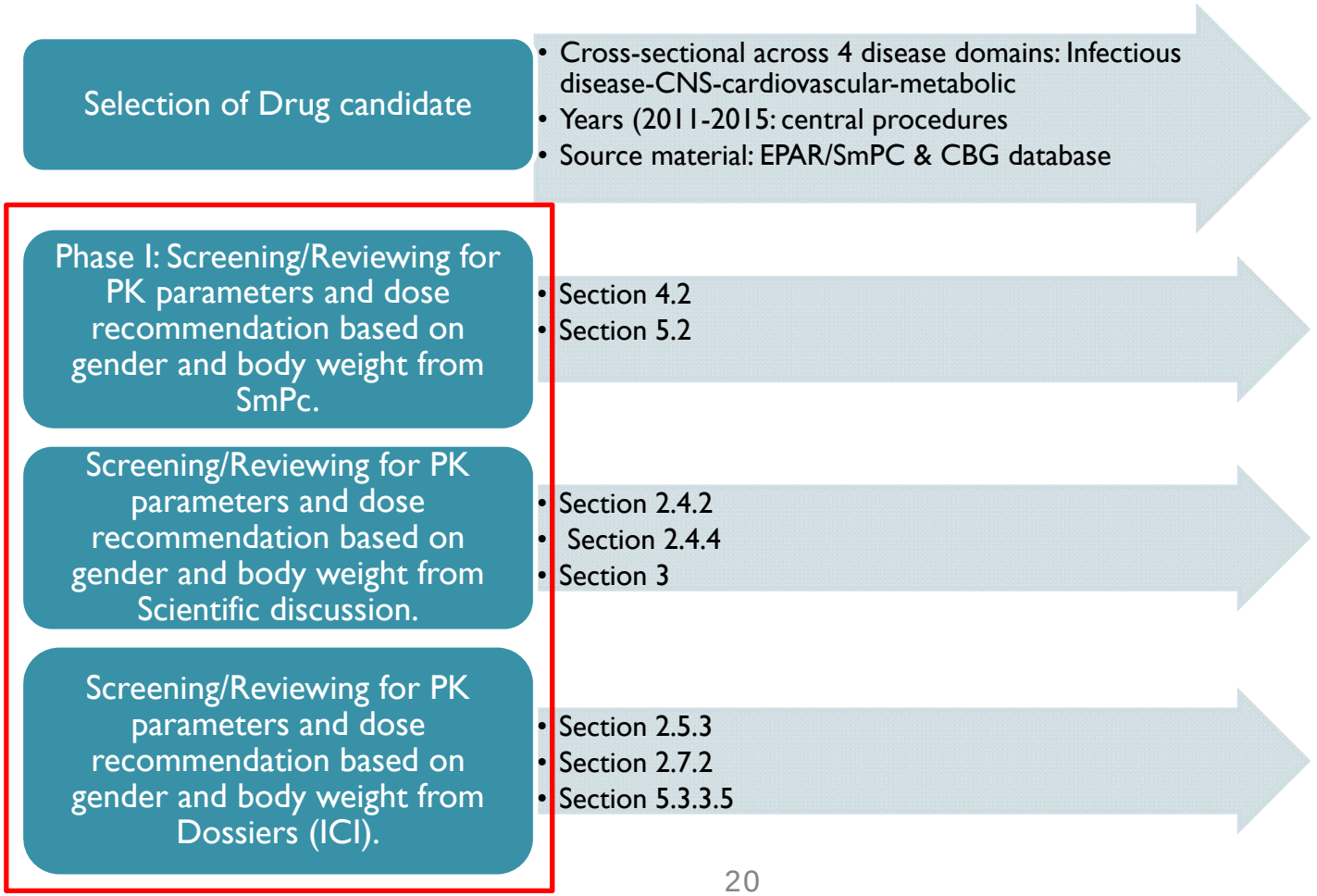
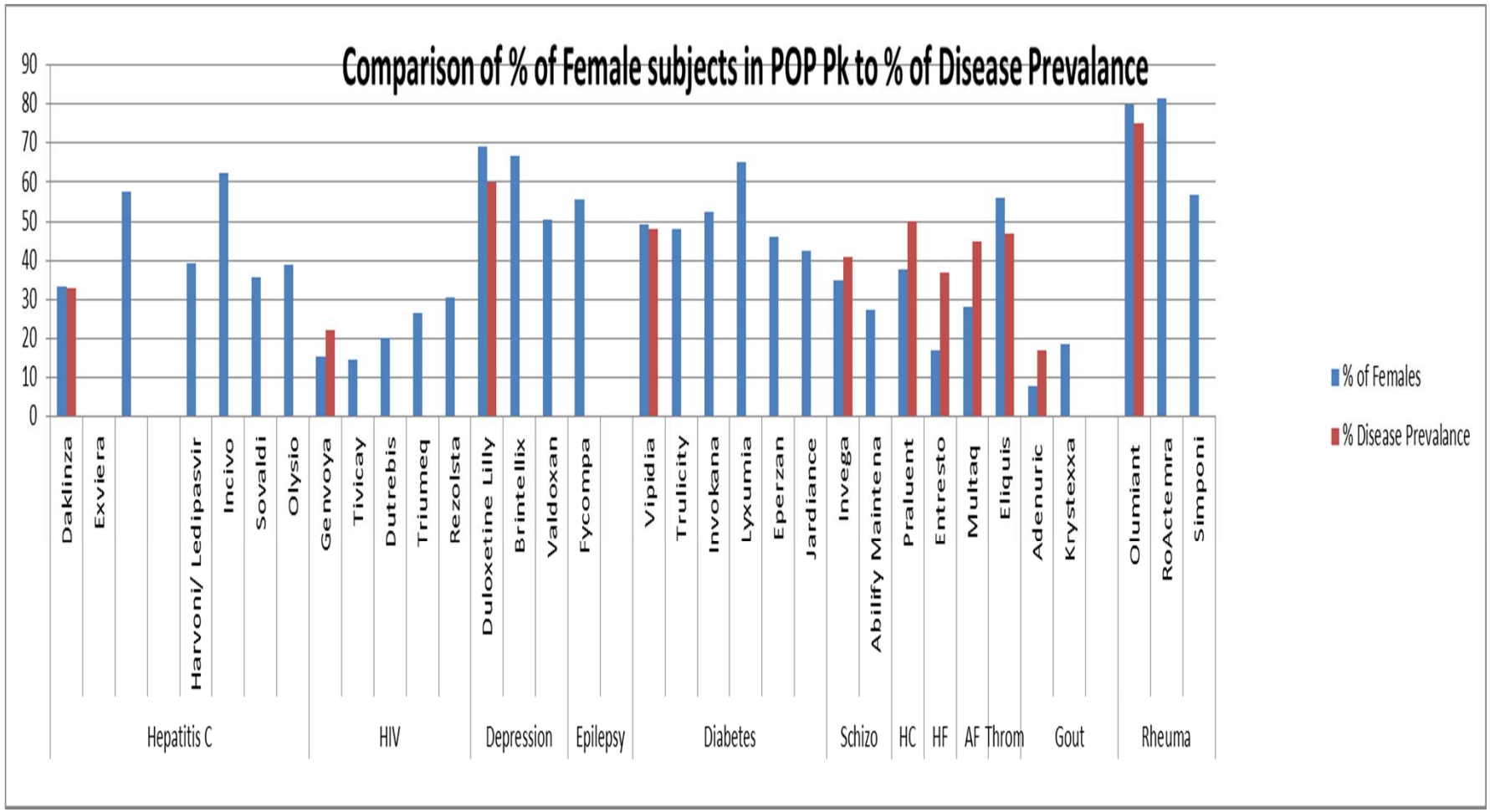
- Information in guidelines is present, but sparse

Phase 1 studies



Gender proportionality phase 1



PK/PD: information in the label

Screening criteria	Score
Dose recommendation based on gender.	0
Dose modification based on body weight.	2
Statistically significant effect on gender, but not clinically relevant. (Daklinza, Exveria, Fycompa, Lyxumia, Multaq)	5
Statistically significant effect on body weight, but not clinically relevant. (Exveria, Harvoni , Fycompa, Eperzan, Trulicity, Lyxumia, Praluent, Multaq)	8

Screening of Drugs (SmPc and Scientific discussion)

PK/PD: information in the Dossier

Screening criteria	Score
Dose recommendation based on gender.	0
Dose modification based on body weight.	0
Drugs with Number of AUC or Cmax values	22
Drugs having Clearance for gender	3
Total drugs with AUC, Cmax or clearance values	25/29

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- Women are included in phase 1 trials, but less compared to phase 3
- PK/PD data in the label lack behind those in the dossier

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Take Home Message: forget numbers, think big

- ❑Discuss with different stakeholders the role of gender in drug development
- ❑Create ‘gender awareness’ among regulators
- ❑Use dossier data to the maximum