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COMMENTARY

Commentary on 'Gender differences in clinical registration trials; is there a real problem?' by Labots *et al.*

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From a European regulator's perspective, we support the need for women to be included in phase 3 trials. It is the current state of the art. The Clinical Trial Directive (CTD) is leading, and current EU guidelines advise on the clinical evidence required for a medicinal product benefit/risk assessment. It is expected that the confirmatory phase 3 trials reflect the population to be treated, once the drug is on the market. As most drugs are not gender specific, women and men are included in most of the confirmatory trials. Studies do not need to be powered for formal subgroup analyses but should allow an estimate of potential differences in efficacy and safety [1]. The EMA concluded their ICH report of 2005, on gender equality in clinical trials, that women were slightly underrepresented in phase 1 and 2 trials, but not phase 3 [2]. A gender-specific guideline was not considered necessary.

Yet the pressure for gender awareness in drug development remains. Rather than the proportion of men and women included in clinical trials, the real question concerns gender differences in response to drugs. New insights into traditional diseases and a focus on personalized medicine has its impact; a better understanding of gender differences in the pathophysiology of diseases requires different approaches in drug development and drug use [3]. The authors rightfully recognize this issue, and gender-sensitive information is still sparse in most labels.

What can be done from a regulator's perspective? First, a broader discussion among the different stakeholders, drug developers, regulators, clinicians, patients, and prescribers is needed to identify what additional useful information should be included in the label.

Second, drug dossier data could be used more extensively as it contains high levels of detailed evidence. In Europe, drug dossier data are translated in the Summary of Product Characteristics (SmPC), leaflet, and the European Public Assessment Reports (EPAR). All information, relevant to the prescriber, user or scientific nonspecialists, should be available. Information on specific subgroups, such as children and elderly, gained attention over the past years. Gender-sensitive information needs to catch up, but it should be relevant to both the user and prescriber.

Third, drug dossier data can be used for regulatory learning, as Labots *et al.* [4] have done when examining whether gender proportionality in drug trials is skewed. Another strategy would be to ask applicants to share individual patient trial data with academia or regulatory scientists, to allow analyses of subgroups and their characteristics [5].

Finally, when drugs enter the market, information on their efficient and safe use is collected in different ways, e.g., through periodic safety update reports (PSUR's), registries, safety reporting databases and scientific publications. Initiatives continue to optimize data sources for all stakeholders [6].

Labots *et al.* give insight into the potential of using drug dossier data for a better understanding of the drug licensing process. Their conclusion on gender proportionality in clinical trials does not ignore that gender awareness in drug development needs attention. How to proceed requires a broader discussion among all stakeholders. Evidently, regulatory science platforms serve this purpose [7, 8].

Competing Interests

There are no competing interests to declare.

References

1 Parliament of the European Union. DIRECTIVE 2001/20/EC. Available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf (last accessed 28 February 2018).

DOI:10.1111/bcp.13620

2 European Medicines Agency. Ich – gender considerations in the conduct of clinical trials. Available at https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500059887.pdf (last accessed 28 February 2018).

3 Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J 2010; 18: 598–602.

4 Labots G, Jones A, de Visser SJ, Rissmann R, Burggraaf J. Gender differences in clinical registration trials: is there a real problem? Br J Clin Pharmacol 2018; 84: 700–7.

5 Welten CC, Koeter MW, Wohlfarth TD, Storosum JG, van den Brink W, Gispen-de Wied CC, *et al*. Early nonresponse in the antipsychotic treatment of acute mania: a criterion for reconsidering treatment? Results from an individual patient data meta-analysis. J Clin Psychiatry 2016; 77: e1117–23.

6 European Medicines Agency. Initiative for patient registries: Strategy and pilot phase. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195576.pdf (last accessed 28 February 2018).

7 Geneesmiddel Debat. Leidende rol Nederland klinisch onderzoek met vrouwen. Available at https://www.geneesmiddelendebat.nl/nieuws/leidende-rol-nederland-klinisch-onderzoek-met-vrouwen/ (last accessed 28 February 2018).

8 CBG-Meb. CBG-Wetenschapsdag: vrouwen goed vertegenwoordigd in klinisch geneesmiddelenonderzoek. Available at https://www.cbg-meb.nl/actueel/nieuws/2018/02/16/cbg-wetenschapsdag-vrouwen-goed-vertegenwoordigd-in-klinisch-geneesmiddelenonderzoek (last accessed 28 February 2018).