Evaluation of Publicly Available Information on Sex-Related Differences in the Efficacy and Safety of Newly Approved Medications

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INTRODUCTION

Safety and efficacy of some drugs may vary by sex[1,2]; rational prescribing requires easy access to reliable information regarding potential sex-based differences. To make such information accessible, the Food and Drug Administration (FDA) released an action plan in 2014 to enhance the collection and availability of demographic subgroup data.[3] The effort emerged from the FDA Safety and Innovation Act (FDASIA) of 2012 and resulted in the updating and creation of new drug information sources such as Drug Trials Snapshots.[4]

Clinicians may expect scientific literature to provide the best evidence regarding sex differences in drugs. However, it is unclear whether publications consistently provide such information, and how this information compares to FDA sources. In this study, we characterize the availability and depth of publicly accessible information across journal publications and FDA sources regarding sex differences in drug safety and efficacy.

METHODS

We analyzed data for all new molecular entities (NMEs) and Therapeutic Biological Products (TBPs) approved by the FDA in 2019 and 2020. We excluded products approved exclusively for a single-sex and those with orphan drug designation (as limited sample sizes preclude identifying sex-based differences).

We reviewed trial publications and three FDA sources (original drug labels, clinical reviews, and Drug Trials Snapshots). Publications were identified via ClinicalTrials.gov.

From each data source, we searched for efficacy/safety data by sex (text, tables, or figures within documents), statements regarding the presence of sex differences (or statement of no difference) in adverse events and primary efficacy outcome, and availability of sex-based dosing recommendations.

Data were extracted by one researcher (KH) and double-checked by a second researcher (ST). Discrepancies were resolved through consensus with an additional researcher.

RESULTS

The FDA approved 101 NMEs/TBPs in 2019 (N=48) and 2020 (N=53). Of these, 62 were excluded (52 were orphan drugs, 5 were exclusively for a single-sex, and 5 were diagnostic products). Thirty-nine drugs met our inclusion criteria, including four breast cancer medicines approved for both sexes. Across 80 pivotal trials with 53,189 trial participants, women comprised 65% of trial participants (Table 1); they were under-represented in some therapeutic areas such as plaque psoriasis and schizophrenia.

Publications were identified and examined for 67 of 80 pivotal trials. (One trial was excluded as it only included women. No publications could be located for 12 trials, and 5 publications included results from multiple trials.)

Safety data by sex was discussed in 100% of FDA clinical reviews and FDA Drug Trials Snapshots, but only 1 of 39 (2.6%) FDA drug labels. No trial publications contained text/tables/figures of safety data by sex. Efficacy data by sex was discussed in 31 of 39 (79.5%) FDA clinical reviews, 39 (100%) FDA Drug Trials Snapshots, 8 (20.5%) FDA drug labels, and 12 (19.4%) trial publications (Table 2).

For all medications in which sex differences in adverse events and primary efficacy outcomes were reported, no dosing recommendations/adjustments based on sex were provided.

DISCUSSION

We found substantial variability in the reporting of information related to potential sex-based differences in drug safety and efficacy across trial publications and FDA sources. Although clinical trial data are a key source of evidence for clinical decision-making, there was no mention of sex effects on safety in any publication analyzed in this study. And only approximately 20% of publications contained information

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Table 1 Descriptive Characteristics of NME and TBP Indications Approved by the U.S. Food and Drug Administration in 2019 and 2020 (Listed in the Order of Approval Date)

Drug name (Generic name)	FDA approval division[a,b]	Indication	Number of pivotal trials[c]	Total participants (% female)
Jeuveau (efinaconazolebotulinum toxin-type A)	DDDP	Glabellar lines associated with corrugator and/or procerus muscle activity	2	654 (91%)
Mayzent (siponimod)	DNP	Relapsing forms of multiple sclerosis	1	1,651 (60%)
Balversa (erdafitinib)	DOP1	Locally advanced or metastatic urothelial cancer	1	87 (21%)
Skyrizi (risankizumab-rzaa)	DDDP	Moderate-to-severe plaque psoriasis	5	2,275 (30%)
Piqray (alpelisib)	DOP1	Advanced breast cancer	1	572 (100%)[d]
Recarbrio (imipenem, cilastatin, and relebactam)	DAIP	Complicated urinary tract infection	2	514 (48%)
Accrufer (ferric maltol)	DHP	Low iron stores	3	295 (68%)
Rinvoq (upadacitinib)	DPARP	Rheumatoid arthritis	5	4,381 (79%)
Xenleta (lefamulin)	DAIP	Community-acquired bacterial pneumonia	2	1,289 (44%)
Nourianz (istradefylline)	DNP	"Off episodes" in patients with Parkinson's disease	4	1,148 (49%)
Ibsrela (tenapanor)	DGIEP	Irritable bowel syndrome with constipation	2	1,199 (82%)
Aklief (trifarotene)	DDDP	Acne vulgaris	2	2,420 (55%)
Beovu (brolucizumab-dbll)	DTOP	Wet age-related macular degeneration	2	1,817 (57%)
Reyvow (lasmiditan)	DNP	Acute migraine with/without aura	2	4,439 (84%)
Fetroja (cefiderocol)	DAI	Complicated urinary tract infection	1	371 (55%)
Xcopri (cenobamate)	DN2	Partial-onset seizures	2	658 (49%)
Padcev (enfortumab vedotin-ejfv)	DO1	Locally advanced or metastatic urothelial cancer	1	152 (29%)
Caplyta (lumateperone)	DP	Schizophrenia	3	1,455 (23%)
Dayvigo (lemborexant)	DP	Insomnia	2	1,955 (78%)
Enhertu (fam-trastuzumab deruxtecan-nxki)	DO1	Metastatic breast cancer	2	234 (100%)[d]
Ubrelvy (Ubrogepant)	DNP	Migraine with/without aura	2	3,358 (88%)
Pizensy (lactitol)	DGIEP	Chronic idiopathic constipation	1	594 (76%)
Nexletol (bempedoic acid)	DMEP	High LDL cholesterol	2	3,009 (29%)
Vyepti (eptinezumab-jjmr)	DN2	Migraines	2	1,960 (86%)
Barhemsys (amisulpride)	DGIEP	Post-operative nausea and vomiting	4	2,751 (87%)
Nurtec ODT (rimegepant)	DN2	Acute migraine	1	1,351 (85%)
Zeposia (ozanimod)	DN2	Multiple sclerosis	2	2,659 (67%)
Trodelvy (sacituzumab govitecan-hziy)	DO1	Breast cancer	1	108 (99%)
Ongentys (opicapone)	DN1	"Off episodes" in patients with Parkinson's disease	2	1,006 (41%)
Byfavo (remimazolam)	DAAP	Starting and maintaining sedation in adults undergoing short procedures	3	966 (52%)
Rukobia (fostemsavir)	DAV	HIV infection	1	371 (22%)
Xeglyze (abametapir)	DDDP	Head lice	2	216 (85%)
Olinvyk (oliceridine)	DAAP	Acute pain	2	790 (92%)
Winlevi (clascoterone)	DDD	Acne vulgaris	2	1,440 (63%)
Sogroya (somapacitan-beco)	DGE	Growth hormone deficiency	1	300 (52%)
Veklury (remdesivir)	DAV	COVID-19	3	2,043 (37%)
Klisyri (tirbanibulin)	DDD	Actinic keratosis	2	702 (13%)
Margenza (margetuximab-cmkb)	DO1	Metastatic breast cancer	1	536 (99%)
Gemtesa (vibegron)	DUOG	Overactive bladder	1	1,463 (85%)
Total			80	53,189 (65%)

Notes: [a]*DAAP, Division of Anesthesia, Addiction Medicine and Pain Medicine; DAIP, Division of Anti-Infective Products; DAI, Division of Anti-Infectives;DAV, Division of Antivirals; DDD, Division of Dermatology and Dentistry; DDDP, Division of Dermatology and Dental Products; DGE, Division of General Endocrinology; DGIEP, Division of Gastroenterology and Inborn Errors Products; DHP, Division of Hematology Products; DMEP, Division of Metabolism and Endocrinology Products; DNP, Division of Neurology Products; DN1, Division of Neurology 1; DN2, Division of Neurology 2; DOP1, Division of Oncology Products 1; DO1, Division of Oncology 1; DP, Division of Psychiatry; DPARP, Division of Pulmonary, Allergy, and Rheumatology Products; DTOP, Division of Transplant and Ophthalmology Products; DUOG, Division of Urology, Obstetrics, and Gynecology*

[b]*In November 2019, the FDA office of new drugs (OND) underwent reorganization and its divisions were re-named. For example, the Division of Oncology Products 1 (DOP1) was renamed as Division of Oncology 1 (DO1), and the Division of Neurology Products was split into Division of Neurology I and II*

[c]*Number of pivotal trials based on FDA medical review documents and Drug Trials Snapshots*

[d]*One male participant was included. Due to rounding, the proportion female reads as 100%*

about sex effects on efficacy. Drug Trials Snapshots always reported on potential sex-based differences in both safety and efficacy. Most clinical reviews did so for safety information (94.9%), and more than half did so for efficacy (64.1%). In contrast, the majority of drug labels provided neither (safety: 2.6%; efficacy: 17.9%); current FDA drug labeling guidance does not specify a requirement to indicate sex-based differences in efficacy or safety.[5,6]

Despite our finding that approximately one-third of drugs are reported to have a sex-based difference in safety, none of the reviewed materials provided clinicians with recommendations on adjusting patient care accordingly, raising questions

Table 2 Availability of Safety and Efficacy Data Pertaining to Sex Differences in Various Trial Documents of NMEs and TBPs Approved by the U.S. Food and Drug Administration in 2019–2020

	FDA drug labels	FDA Drug Trials Snapshots	FDA clinical review documents	Trial publications
Total sources evaluated	39	39	39	62[a,b]
Safety				
Text, table, or figure discussing or displaying safety data by sex	1 (2.6%)	39 (100%)	39 (100%)	0 (0%)
Text discussing sex-based differences (or statement of no difference) in adverse events	1 (2.6%)	39 (100%)	37 (94.9%)	0 (0%)
Sex-based difference exists[c]	0 (0%)	0 (0%)	11 (29.7%)	0 (0%)
Sex-based difference does not exist	1 (100%)	33 (84.6%)	17 (46.0%)	0 (0%)
Unclear whether or not a sex-based difference exists	0 (0%)	6 (15.4%)	9 (24.3%)	0 (0%)
Efficacy				
Text, table, or figure discussing or displaying efficacy data by sex	8 (20.5%)	39 (100%)	31 (79.5%)	12 (19.4%)
Text discussing sex-based differences (or statement of no difference) in efficacy (on primary outcome)	7 (17.9%)	39 (100%)	25 (64.1%)	10 (16.1%)
Sex-based difference exists[c]	0 (0%)	0 (0%)	4 (16.0%)	1 (10%)
Sex-based difference does not exist	7 (100%)	31 (79.5%)	19 (76.0%)	8 (80%)
Unclear whether or not a sex-based difference exists	0 (0%)	8 (20.5%)	2 (8.0%)	1 (10%)

Notes: [a]*There were more (n=62) trial publications than for example FDA medical reviews (n=39) because many NMEs and TBPs approvals are supported by multiple trials, which are published individually*
[b]*Not all 80 pivotal trials listed in Table 1 were published according to ClinicalTrials.gov. Also, one trial only included a single sex and therefore was excluded from the study. Data from 67 (84%) pivotal trials (62 trial publications) were included and examined*
[c]*We considered sex-based difference exists when the sources state there are differences by sex, even if the FDA deemed the difference needs further evaluation or is not yet conclusive. Drugs with sex-based differences in adverse events include Balversa, Recarbrio, Accrufer, Rinvoq, Nourianz, Xcopri, Dayvigo, Pizensy, Barhemsys, Zeposia, and Byfavo. Drugs with sex-based differences in efficacy include Ubrelvy, Nexletol, Barhemsys, Nurtec ODT, and Sogroya*

about the actionability of the information. As clinicians rely on different sources of medical evidence to make informed treatment decisions, we recommend that sex analyses of drug efficacy and safety be conducted and explicitly reported in trial publications, and that significant safety and efficacy signals be consistently noted in all sources of FDA information.

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Data Availability: *The datasets generated and/or analyzed during the current study are freely available in the Zenodo repository (https://doi.org/10.5281/zenodo.5799493).*

Declarations:

Conflict of Interest: *PD has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018), and grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-2020); and is an editor at The BMJ. KH was supported in 2020 by the FDA of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD005946 totaling US$5,000 with 100% funded by FDA/HHS. The project contents are those of KH and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS, or the U.S. Government. HH is currently employed by and has stock ownership in Regeneron Pharmaceuticals. He was previously employed by the FDA and received a grant to support this work through University of Maryland M-CERSI; 2020. ST declares no COI.*

REFERENCES

1. Feuerstein IM, Jenkins MR, Kornstein SG, Lauer MS, Scott PE, Raju TNK, et al. Working together to address women's health in research and drug development: summary of the 2017 Women's Health Congress Preconference Symposium. J Womens Health. 2018;27(10):1195–203.
2. Prakash VS, Mansukhani NA, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias in interventional clinical trials. J Womens Health. 2018;27(11):1342–8.

3. The U.S. Food and Drug Administration. FDA action plan to enhance the collection and availability of demographic subgroup data [Internet]. 2014 [cited 2021 Dec 10]. Available from: https://www.fda.gov/media/89307/download
4. Downing NS, Shah ND, Neiman JH, Aminawung JA, Krumholz HM, Ross JS. Participation of the elderly, women, and minorities in pivotal trials supporting 2011–2013 U.S. Food and Drug Administration approvals. Trials. 2016;17(1):199.
5. The U.S. Food and Drug Administration. Guidance for industry: dosage and administration section of labeling for human prescription drug and biological products - content and format [Internet]. 2010 [cited 2021 Jul 8]. Available from: https://www.fda.gov/media/72142/download
6. The U.S. Food and Drug Administration. Guidance for industry: indications and usage section of labeling for human prescription drug and biological products - content and format [Internet]. 2018 [cited 2021 Jul 12]. Available from: https://www.fda.gov/media/114443/download