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

Safety and efficacy of some drugs may vary by sex\cite{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.\cite{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.\cite{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 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
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 | Indication | Number of pivotal trials | Total participants (%) | Female |
|--------------------------|-----------------------|------------|--------------------------|------------------------|--------|
| Jeuveau (efinacozomab)    | 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 (erdaltimib)    | DOP1                  | Locally advanced or metastatic urothelial cancer | 1                       | 87 (21%)             |        |
| Skyrizi (risankizumab-raa) | DDDP              | Moderate-to-severe plaque psoriasis | 5                       | 2,275 (30%)           |        |
| Pqray (alpelisib)        | DP                   | Advanced breast cancer | 1                       | 572 (100%)           |        |
| Recarbrio (nimipenem, cilastatin, and relbatam) | 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 (lefatimulin)    | 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                       | 2,817 (57%)           |        |
| Reyvox (lasmiditan)      | DNP                  | Acute migraine with/without aura | 2                       | 4,439 (84%)           |        |
| Fetroxa (celfiderocol)   | DA1                  | 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 (limborexant)    | DP                   | Insomnia | 2                       | 1,955 (78%)           |        |
| Enhetru (fam-trastuzumab derustecan-nxki) | DDDP                 | Metastatic breast cancer | 2                       | 234 (100%)           |        |
| Uberly (ubrogepant)      | DNP                  | Migraine with/without aura | 2                       | 3,358 (88%)           |        |
| Pizensy (lactitol)       | DGIEP                | Chronic idiopathic constipation | 1                       | 594 (76%)             |        |
| Nextrol (bempedoic acid) | DMEP                 | High LDL cholesterol | 2                       | 3,009 (29%)           |        |
| Vyepti (epineuzumab-jmrr) | DN2                | Migraines | 2                       | 1,960 (86%)           |        |
| Barhemsys (amisulpride)  | DGIEP                | Post-operative nausea and vomiting | 4                       | 2,751 (87%)           |        |
| Nutre (ODT) (limegpran)  | DN2                  | Acute migraine | 1                       | 1,351 (85%)           |        |
| Zeposia (ozanomad)       | DN2                  | Multiple sclerosis | 2                       | 2,659 (67%)           |        |
| Tedvelcy (salcztuzumab govetucan-hzi) | DO1            | Breast cancer | 1                       | 108 (99%)             |        |
| Öngentys (opicupone)     | 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 (fostemsvavir)   | DAV                  | HIV infection | 1                       | 371 (22%)             |        |
| Xgege (abametapir)       | DDDP                 | Head lice | 2                       | 216 (85%)             |        |
| Olimyvyk (olicercidine)  | 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)   | DDI                  | Acute keratitis | 1                       | 702 (13%)             |        |
| Margenza (margetuximab-cmkb) | DO1          | Metastatic breast cancer | 1                       | 536 (99%)             |        |
| Gentesa (vigeborg)       | DUOG                 | Overactive bladder | 1                       | 1,463 (85%)           |        |
| Total                    |                      |              | 80                      | 53,189 (65%)          |        |

Notes: aDAAP, 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; DDP, 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; D1, Division of Neurology I and II; 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.

bIn 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.

cNumber of pivotal trials based on FDA medical review documents and Drug Trials Snapshots.

dOne male participant was included. Due to rounding, the proportion female reads as 100%.

eAbout 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...
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.57990493).

**Declarations:**

Conflict of Interest: PD has received travel funds from the European Respiratory Society (2012) and UpRoyal 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.

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