Study of Sex Differences in the Clinical Evaluation of Medical Products
Guidance for Industry

DRAFT GUIDANCE

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Study of Sex Differences in the Clinical Evaluation of Medical Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for (1) increasing enrollment of females in clinical trials[2] and non-interventional studies to help ensure the generalizability of results, (2) analyzing and interpreting sex-specific data, and (3) including sex-specific information in regulatory submissions of medical products.[3] Historically (Sosinsky et al. 2022), fewer females than males have been included in clinical trials[4] of medical products, which has led to a lack of information available for females and their health care providers regarding the benefits and risks of such

[1] This guidance has been prepared by the Center for Drug Evaluation and Research and the FDA Office of Women's Health in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Office of Clinical Policy, and the Oncology Center of Excellence at the Food and Drug Administration.

[2] Sponsors may be required to develop or submit information regarding the representativeness of clinical study participants. For example, the Federal Food, Drug, and Cosmetic (FD&C) Act, as amended by section 3601(b) of the Food and Drug Omnibus Reform Act of 2022 (FDORA), enacted as part of the Consolidated Appropriations Act, 2023 (Public Law 117-328)), requires sponsors to submit to FDA diversity action plans for certain studies of medical products. The diversity action plans must specify the sponsor's rationale and goals for clinical study enrollment, disaggregated by sex, age group, race, and ethnicity, and describe how the sponsor intends to meet those goals. See section 505(z)(2) of the FD&C Act for drugs and section 520(g)(9)(B) of the FD&C Act for devices. For more information on the required submission of enrollment goals by sex for certain clinical studies, see the draft guidance for industry *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* (June 2024) (when final, this guidance will represent FDA's current thinking on this topic). Per section 3602(c) of FDORA, the requirement to submit a diversity action plan applies to certain clinical studies for which enrollment commences after 180 days from the publication of the final guidance. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the purposes of this guidance, a *medical product* is a drug, biological product, or medical device intended for humans.

[4] For the purposes of this guidance, a *clinical trial* or an *interventional study* is a study in which participants, either healthy volunteers or volunteers with the condition or disease being studied, are assigned to one or more interventions, according to a study protocol, to evaluate the effects of those interventions on subsequent health-related outcomes.

medical products in females. Over recent decades, there has been an increase in the representation of females in clinical trials for drugs[5] and devices,[6,7] with greater availability of sex-specific data. However, females remain underrepresented in some therapeutic areas (see, e.g., Zhou et al. 2024), which can make it challenging to evaluate the benefits and risks of medical products for females in these therapeutic areas (see, e.g., Zhou et al. 2023; Scott et al. 2018). In areas where males may be underrepresented in clinical trials, the general principles outlined in this guidance also apply to increasing enrollment of males in clinical trials.

When finalized, this guidance will replace the guidance titled *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*, issued in July 1993.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Terminology

While, over time, the terms sex and gender have often been used interchangeably in the scientific literature, media, and FDA guidance and regulations, the constructs of sex and gender have evolved into separate concepts with distinct definitions that should be used consistently in the design, conduct, analysis, and reporting of data from clinical trials and non-interventional[8] studies submitted to FDA. For the purposes of this guidance, the following definitions are used to distinguish sex and gender:

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[5] For the purposes of this guidance, references to *drugs* and *drug and biological products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) that are regulated as drugs.

[6] For the purposes of this guidance, references to *devices* refer to products that meet the definition of a medical device per section 201(h) of the FD&C Act and are not otherwise deemed to be a drug under section 503(h) of the FD&C Act.

[7] For more information on sex and gender considerations in the study of medical devices, see the draft guidance for industry and FDA staff *Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies* (January 2025). When final, this guidance will represent FDA's current thinking on this topic. See also the guidance for industry *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993).

[8] For the purposes of this guidance, a *non-interventional study* is a type of drug or biological study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol. See the draft guidance for industry *Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products* (March 2024). When final, this guidance will represent FDA's current thinking on this topic.

- **Sex** is a biological construct based on anatomical, physiological, hormonal, and genetic (chromosomal) traits. Sex is generally assigned based on anatomy at birth and is usually categorized as female or male, but variations occur. Variations of sex refers to differences in sex development or intersex traits.[9]

- **Gender** is a multidimensional construct that encompasses how an individual self-identifies. Gender may be described across a continuum, may be nonbinary, and may change over the course of a lifetime. Gender may or may not correspond to a person's sex assigned at birth (National Academies of Sciences, Engineering, and Medicine 2022).

For many drug and device trials, the term gender is used as a substitute for biological sex. In most cases, a participant's sex and gender are concordant, but FDA recognizes that sex and gender are not always concordant. Although sex and gender are distinct concepts, they may both influence etiology and presentation of disease and affect treatment and patient-reported outcomes. This guidance focuses on biological differences that can impact outcomes in clinical trials and non-interventional studies and therefore focuses on sex. However, FDA also encourages sponsors to consider whether gender differences are relevant to a specific study and should be factored into the study design and analysis.

For the purposes of this guidance, we use the terms *male* and *female* to refer to biological sex assigned at birth, and *male* and *female* will represent distinct biological categories. It may be appropriate to include a separate category for intersex in clinical trials and non-interventional studies and to collect data on individuals for whom the development of chromosomal, gonadal, or anatomic sex is atypical. Further discussion of the inclusion of intersex individuals is beyond the scope of this guidance.

B. Data Standards

Trial data standards provide a consistent general framework for organizing and reporting trial data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.[10] For drug and biological product submissions subject to section 745A(a) of the FD&C Act,[11] data format specifications for the tabulation of datasets in study data are consistent with the standards established by the Clinical Data Interchange

[9] See Measuring Sex, Gender Identity, and Sexual Orientation for the National Institutes of Health, available at https://www.nationalacademies.org/our-work/measuring-sex-gender-identity-and-sexual-orientation-for-the-national-institutes-of-health. Intersex refers to the state of being born with biological sex characteristics that vary from what is typically thought of as exclusively male or female. See Griffiths 2018.

[10] See Study Data for Submission to CDER and CBER, available at https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber.

[11] See section 745A(a) of the FD&C Act discussing requirements of standardized study data for electronic submissions of certain investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and certain biologics license applications (BLAs).

Standards Consortium (CDISC).[12] The CDISC defines sex as the "[p]henotypic expression of chromosomal makeup that defines a study subject as male, female, or other." For trial data submitted to FDA, the *sex* variable should reflect the sex assigned at birth of each participant to be consistent with the CDISC definition.[13]

FDA recommends that participants (not the team conducting the trial) self-report sex information, which is generally based on their sex assigned at birth. However, if a participant is unable to self-report their sex (e.g., because of the participant's inability to respond), other sources can be used by the team conducting the trial to collect this information.

Unlike the sex variable, gender is currently not a required data variable for submissions subject to 745A(a) of the FD&C Act[14] and is not currently a standardized data field in CDISC. FDA encourages inclusion of gender data particularly if gender may influence the outcome of interest. FDA recommends discussing the incorporation of data on gender with the appropriate review division.[15]

C. Representation of Female Participants in Clinical Trials and Non-Interventional Studies

For many years, FDA has encouraged representation of females in clinical trials submitted to FDA. In 1993, FDA issued the guidance *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (1993 guidance) to increase participation of females in early phase (dosing) trials (see, e.g., Zhou et al. 2023; Scott et al. 2018).[16] While the 1993 guidance uses the term *women* when referring to female sex, this guidance uses the term *female*. For definitions of sex and gender, see section II.A of this guidance.

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[12] See the guidance for industry *Providing Regulatory Submissions in Electronic Format – Standardized Study* Data (June 2021) and the technical specifications document *Study Data — Technical Conformance Guide* (March 2024); see also CDISC Glossary Controlled Terminology, 2022-12-16, available at https://evs.nci.nih.gov/ftp1/CDISC/Glossary/CDISC%20Glossary.pdf.

[13] For more information on the collection and submission of sex- and gender-specific data for medical device submissions, please see the draft guidance for industry and FDA Staff *Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies*.

[14] See the guidance for industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data* and the technical specifications document *Study Data — Technical Conformance Guide*.

[15] FDA invites sponsors to discuss their proposals with the appropriate review division. See also the draft guidance for industry *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies*. For more information on the collection and submission of sex- and gender-specific data for medical device submissions, please see the draft guidance for industry and FDA staff *Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies*.

[16] See the guidance for industry *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993). In 2014, FDA's Center for Devices and Radiological Health issued a guidance for devices regarding sex-specific patient enrollment, data analysis, and reporting of study information. See the draft guidance for industry and FDA staff *Evaluation of Sex-Specific Data in Medical Device Clinical Studies.*

In 1998, FDA issued regulations collectively known as the "Demographic Rule,"[17] which require, in part, that sponsors include in their annual reports for drugs and biological products being studied under an investigational new drug application (IND), the number of participants entered into the study to date tabulated by age group, gender,[18] and race.[19] The Demographic Rule also requires the presentation of safety and effectiveness data in the clinical data section of a new drug application (NDA) by "gender, age, and racial subgroups"[20] and identification of any modifications of dose or dose interval needed for specific subgroups.[21]

In 2000, FDA amended its regulations in 21 CFR part 312 to state that FDA may place a proposed or ongoing clinical investigation under an IND on clinical hold if (1) the study is for a drug for the treatment of a life-threatening disease or condition that affects both females and males, and (2) females or males of reproductive potential[22] with the disease or condition being studied are excluded from eligibility because of a risk or potential risk of reproductive or developmental toxicity, subject to three exceptions.[23]

Along with the evolution of FDA's policies regarding the inclusion of females in clinical research, there has been an increase in overall representation of female participants in clinical trials.[24] However, female participants remain underrepresented in clinical trials for some therapeutic areas where the disease or condition affect both males and females (see Zhou et al. 2024; Sosinsky et al. 2022; Scott et al. 2018), and there are opportunities to enhance representation of females, as appropriate for answering the scientific question. Generally, males have not been underrepresented in clinical trials compared to the prevalence of the disease or

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[17] 1998 Demographic Rule – "Amendments to Content and Format of a New Drug Application" (21 CFR 314.50 (d)(5)). The 1998 Demographic Rule, or New Drug Application (NDA) Content and Format Regulations, was published in the *Federal Register* on February 11, 1998 (63 FR 6854).

[18] While the Demographic Rule uses the term *gender* when referring to sex, this guidance uses the term *sex* as defined in section II.A of this guidance.

[19] 21 CFR 312.33(a)(2).

[20] 314.50(d)(5)(v) and (vi).

[21] 21 CFR 314.50(d)(5)(v) and (vi). While 21 CFR 314.50 does not apply to BLAs, FDA recommends presenting demographic data in those applications the same way that demographic data is presented in NDAs. In addition, while 21 CFR 314.50 does not apply to medical device submissions, the recommendations in this guidance may help sponsors of clinical investigations of devices meet certain applicable legal requirements. For example, an investigational plan must include a description of the patient population, including sex (see 21 CFR 812.25(c)), and a premarket approval application is required to include information about study population (see 21 CFR 814.20(b)(3)(v)(B) and (b)(6)(ii)).

[22] While 21 CFR 312.42(b)(1)(v) uses the term "men or women with reproductive potential," we consider that term in the regulation to mean "males or females with reproductive potential" consistent with the terms as defined in section II.A of this guidance.

[23] 21 CFR 312.42(b)(1)(v).

[24] See 2015–2019 Drug Trials Snapshots Summary Report, available at https://www.fda.gov/media/143592/download.

condition in males in the U.S. population. As previously noted, in areas where males may be underrepresented in clinical trials, the general principles outlined in this guidance also apply to increasing enrollment of males in clinical trials.

D. Why Consider Sex Differences in Medical Product Development?

Differences in physiology between females and males can lead to differences in disease manifestations, as well as differences in the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of medical products (Madla 2021). Consequently, it is important to characterize the impact of sex as part of medical product development to determine if there may be differences in PK, PD, effectiveness, and/or safety associated with use of the medical product. Identification of a clinically relevant difference by sex may inform a benefit-risk assessment and inform product labeling. Assessment of sex differences should occur throughout drug development, and in Phase 1 studies, females should be enrolled to determine if there are PK differences by sex that warrant further study.[25]

Sex differences in PK and PD may arise from physiological (e.g., hormonal, body composition), anatomical (e.g., body size), and/or genetic factors. For example, females eliminate zolpidem (the active ingredient in certain FDA-approved drug products indicated to treat certain patients with insomnia) from their bodies more slowly than males, so FDA-approved labeling for such products recommends a lower starting dosage in females.[26] Dynamic fluctuations associated with hormonal changes (e.g., onset of puberty, menstrual cycle, menopause, hormonal contraceptive, hormone therapy use) may also influence clinical outcomes. The risks associated with medical product use may differ by sex, as observed with left ventricular assist devices where females have a higher risk for right ventricular failure, stroke, other neurologic complications, arrhythmias, bleeding, and thrombosis (Sherazi et al. 2017).

In addition, covariates that are uniquely or more commonly associated with a certain sex (e.g., pre- or post-menopause) may account for differences observed regarding the safety or effectiveness of a medical product. For further discussion on statistical considerations for analyzing potential differences among treatment populations, see section IV of this guidance.

[25] While historically an issue more common to females, males have also faced exclusion from clinical studies on the basis of their sex. See the guidance for industry *Male Breast Cancer: Developing Drugs for Treatment* (August 2020).

[26] See Questions and Answers: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended dosages for certain drugs containing zolpidem (e.g., Ambien, Ambien CR, Edluar, and Zolpimist), available at https://www.fda.gov/drugs/drug-safety-and-availability/questions-and-answers-risk-next-morning-impairment-after-use-insomnia-drugs-fda-requires-lower#q2. The prescribing information for Ambien, in which zolpidem is the active ingredient, recommends that "an initial dose is a single dose of 5 mg for women and a single dose of 5 or 10 mg for men." Ambien [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2008.

III. CLINICAL TRIAL DESIGN AND CONDUCT

Trials should be designed to enroll sufficient numbers of females and males to reflect the prevalence of the disease or condition for which the medical product is being investigated to help ensure the generalizability of results and facilitate exploration of potential differences in effects by sex.[27] In considering a specific development program, sponsors should have an understanding of the underlying biology of the disease or condition to anticipate sex differences in PK, PD, and safety and effectiveness. Throughout the drug and biological product development program, sponsors should utilize population PK analyses,[28] and exposure-response analyses to help evaluate sex differences in PK and PD.[29]

A. Recruitment, Enrollment, and Retention

Factors associated with the female sex may impact clinical trial enrollment.[30] Potential participants who are pregnant and/or lactating may be excluded from studies based on the safety profile and teratogenicity of the medical product. Some trials contain contraception requirements, which may limit the enrollment of females of reproductive potential who prefer not to use contraception.

Sponsors should evaluate whether the demographic distribution of the potential trial population changes across different key time points (e.g., at screening, including evaluation of trial inclusion/exclusion criteria; after consent; and at various follow-up time points) and whether these changes have an impact on trial participation (National Institutes of Health 2015). For example, if the proportion of females drops significantly after screening for inclusion/exclusion criteria, this may suggest a need to reexamine the inclusion/exclusion criteria. Removing or limiting unnecessary criteria could improve the participation rates of females in the trial. Sponsors should also consider consulting with academic institutions, health organizations that focus on female health (including community-based organizations), and contract research organizations to determine practices best suited to reducing enrollment and retention challenges.

[27] The recommendations in section III.A of this guidance focus on increasing the enrollment of females in clinical trials for those diseases or conditions in which females have been underrepresented compared to the prevalence of the disease or condition in females in the United States. In general, males have not been underrepresented in a lower proportion compared to the prevalence of a disease in clinical trials. For approaches on enhancing clinical study diversity in broader populations, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[28] See the guidance for industry *Population Pharmacokinetics* (February 2022).

[29] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (May 2003).

[30] See Zhou et al. 2023 and Zhou et al. 2024.

Sponsors should also engage with the patient community to help develop strategies for addressing enrollment and retention challenges.[31]

FDA encourages the following practices to improve the recruitment, enrollment, and retention of females[32] in clinical trials:[33]

- Identify sites where recruitment of females can be facilitated (e.g., clinics or social media sites that target females).
- Consider flexibility in follow-up visit scheduling to allow various opportunities that match participants' schedules, which can include evenings and weekends.
- Ensure that clinical trial sites include geographic locations within the neighborhoods where patients receive their health care.
- Consider the use of mobile medical professionals, such as nurses and phlebotomists, to visit participants at their locations instead of requiring participants to visit clinical trial sites.[34]
- Consider using a digital health technology[35] to collect information directly from participants at their locations rather than having to travel to trial sites.[36]

[31] See the guidance for industry, FDA staff, and other stakeholders *Patient Engagement in the Design and Conduct of Medical Device Clinical Studies* (January 2022). For more information on community and patient engagement strategies, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs*.

[32] For diseases or conditions where males may be underrepresented, the recommendations in this section are applicable to males as well.

[33] While this guidance is focused on sex, many of the recommendations in this section can be applied to the recruitment, enrollment, and retention of other demographic groups (e.g., older adults, persons with disabilities). For more information on and recommendations for making clinical trials more accessible for all populations, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs*.

[34] Ibid.

[35] For the purposes of this guidance, a *digital health technology* is a system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products. For more information, see the guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023).

[36] See the guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018), which provides recommendations on the use of electronic health record data in FDA-regulated clinical investigations.

- Consider providing support services such as childcare or elder care during trial visits.

- Enroll females of different ages, races, ethnicities, hormonal statuses (e.g., menopausal), and comorbidities, as applicable.

- Enroll females of reproductive potential, with appropriate risk mitigation efforts (e.g., contraception) to avoid pregnancy during clinical study participation if the drug or device being studied could potentially harm the fetus, as applicable.

- For diseases or conditions that can occur in both females and males but rarely occur in one of the sexes in actuality,[37] avoid arbitrary exclusion criteria that prohibit participation based on sex.

B. Trial Design

For most drugs and devices, males and females should be included in clinical trials in numbers adequate to allow for reliable benefit-risk assessments and to understand any potential sex-related differences in medical product response. Sponsors of certain clinical investigations must submit a diversity action plan with goals for study enrollment, disaggregated by sex, among other demographic characteristics,[38] and should consider the following recommendations:

- In a trial where there may be a plausible biological reason to expect a different response in females and males to the medical product, the numbers of females and males representing the prevalence/incidence of the disease or condition may not be sufficient to evaluate a sex difference in medical product safety or efficacy. Where sex differences are anticipated, there should be sufficient numbers to inform reliable benefit-risk assessments in males and females.[39] Sponsors should consult with the appropriate FDA review division to consider target enrollment of female and male participants. For more information, see section IV.E of this guidance.

  - Trials to understand sex differences in medical product effectiveness or safety should consider analyzing data by underlying factors of interest. For example, research questions could be framed to assess whether observed sex differences are the result of differences in PK, PD, adherence, comorbidities, or other factors.

  - Trial protocols should include collection of information on other variables (e.g., smoking, age, weight) that may be important in evaluating and understanding sex

[37] See the guidance for industry *Male Breast Cancer: Developing Drugs for Treatment*.

[38] See section 505(z) and 520(g)(9) of the FD&C Act and section 3602 of FDORA. See also the draft guidance for industry *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies*.

[39] For more information, see section IV of this guidance — Statistical Concepts.

differences because these variables may affect drug absorption, distribution, metabolism, and excretion.[40]

C. Enrollment of Participants Who Are Pregnant and/or Lactating

- Sponsors should consider the benefits and risks of enrolling pregnant or lactating participants at various stages of the development program for products not being developed for pregnancy-specific or lactation-specific indications.[41] Potential participants who are pregnant and/or lactating may be excluded from studies based on the safety profile (teratogenicity) of the medical product. As for all participants, when seeking informed consent from pregnant and/or lactating participants, a description of any reasonably foreseeable risks or discomforts must be provided.[42] FDA can require a postmarketing study when applicable criteria are met, including to assess a known serious risk or signals of a serious risk or to identify an unexpected serious risk when data indicate the potential for a serious risk related to individuals who are pregnant or lactating.[43]

- In trials where there is a scientific justification for excluding pregnant participants, consider including PK sampling[44] to inform drug dosing in participants who become pregnant during a trial and can safely remain in the trial. Whether a participant who becomes pregnant during a trial can remain in the trial depends, among other things, on whether the risks to the participant and fetus of continued trial participation are reasonable in relation to the anticipated benefits and the importance of the knowledge that may be expected to result. For pregnant patients who can remain in the trial, PK sampling may provide important information regarding drug disposition during pregnancy, across the trimesters, when physiology can change significantly.

- For participants who become pregnant during a drug and biological product clinical trial but cannot safely continue in the trial, it can be informative to collect relevant PK data

[40] Ibid.

[41] See the draft guidances for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018) and *Clinical Lactation Studies: Considerations for Study Design* (May 2019). When final, these guidances will represent FDA's current thinking on these topics.

[42] 21 CFR 50.25(a)(2)

[43] For drugs, see section 505(o)(3) of FD&C Act. See also the draft guidance for industry *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019) and the draft guidance for industry *Postapproval Pregnancy Safety Studies* (May 2019). When final, these guidances will represent FDA's current thinking on these topics. For devices, see the guidance for industry and FDA staff *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval* (April 2015).

[44] See the draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling* (October 2004). When final, this guidance will represent FDA's current thinking on this topic.

even when the investigational medical product is discontinued. Sponsors can assess PK after the last use of the medical product.

IV. STATISTICAL CONCEPTS

A. Overview[45]

Analyzing sex differences in medical product performance is an important component of assessing product safety and effectiveness and can inform what goes in the product labeling to improve patient care. Analyzing sex differences may involve (1) characterizing the treatment effects for females and for males and any clinically relevant differences or potential differences in those treatment effects, (2) determining whether the product provides greater benefits or risks for a particular sex, (3) determining whether particular benefits or risks exist only for a particular sex, (4) determining how relevant the treatment effect for a particular sex is to understanding the treatment effect for another sex. Apparent sex differences may result in the need to mitigate clinically significant differences in safety or effectiveness between females and males.[46]

The optimal analysis approach will depend on the type of inference that is sought. For example, different approaches may be appropriate for characterizing potential differences in treatment effects between sexes in contrast to estimating the treatment effect within a given sex. Sex is one of many potential demographic characteristics typically evaluated in subgroup analyses of a clinical trial or non-interventional study. When many subgroup analyses are performed, some of the estimated treatment effects may represent random highs and random lows, being far above or far below the respective underlying subgroup treatment effect. Observed differential treatment effects by sex may also be due to other factors associated with sex. For example, the size of the treatment effect may depend on age and weight; distributions for age and weight may be notably different between females and males.

In general, sponsors should plan and conduct analyses to evaluate and understand potential heterogeneity of treatment effects by sex on key effectiveness and safety endpoints. This should include analyses for differences in treatment effects and to estimate treatment effects in females and males. Considerations and recommendations related to these two different types of analyses are provided in sections IV.B and C below. In many cases, it may be beneficial to conduct analyses for individual trials or studies but also combine results across similarly designed trials and studies. Analyses of integrated data from multiple trials or studies should stratify by trial or study. Such analyses may have greater precision and power than analyses of individual trials and

[45] For more information on statistical considerations for clinical studies, see the International Council for Harmonisation (ICH) guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998). See also the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[46] See FDA's web page Impact Story: Using innovative statistical approaches to provide the most reliable treatment outcomes information to patients and clinicians, available at https://www.fda.gov/drugs/regulatory-science-action/impact-story-using-innovative-statistical-approaches-provide-most-reliable-treatment-outcomes.

studies and may be appropriate if meaningful differences in treatment effects are not expected across trials and studies.

B. Analyses for Differences in Treatment Effects Between Females and Males

Analyses to evaluate differences in treatment effects between females and males should include calculation of an estimated difference in treatment effects, along with associated uncertainty (e.g., a 95% confidence interval (CI) for the difference). Such analyses can also include a test for a quantitative interaction of treatment by sex (i.e., a test for whether the treatment effect is larger for females or for males (the two-sided alternative hypothesis) or whether those treatment effects are similar (the null hypothesis)).

Unless the clinical trial or study provides statistical power near 100% for demonstrating a positive average treatment effect in the overall population (which is unlikely), statistical tests for detecting plausible magnitudes of differences in treatment effects by sex (i.e., tests of a treatment-by-sex interaction) tend to be underpowered. The 95% CI for the difference in treatment effects by sex may be very wide and may include large differences. In many cases, the test for a treatment-by-sex interaction may only have sufficient power to detect large differences in treatment effects by sex. There may be insufficient power for some smaller, but still clinically important, differences in treatment effects by sex. Therefore, lack of statistical significance when testing for differing treatment effects by sex is not evidence of absence of a clinically meaningful difference in treatment effects by sex. See Section III.B, Trial Design.

For some clinical trials and non-interventional studies, there may be adequate power for statistical tests of treatment effects using sex-specific subgroup data and for testing the interaction of treatment-by-sex. In general, the power for a test of a treatment-by-sex interaction tends to be larger the more similar the subgroup sizes of females and males. Notably, trials and studies often involve the evaluation of differences in treatment effects by many factors beyond sex, including by demographic factors such as age, race, and ethnicity and by important disease characteristics. The risk of incorrectly concluding that a treatment-by-factor interaction exists increases as the number of factors increases if such tests are performed without adjusting significance levels for the multiple tests.[47]

C. Analyses to Estimate Treatment Effects in Females and Males

Analyses should be planned and conducted to estimate treatment effects and corresponding uncertainty (i.e., a 95% CI) in females and males. Traditionally, only data from a given sex have been used when estimating the treatment effect size for that sex. Sponsors should consider prespecified statistical approaches that incorporate the data from all participants when estimating the treatment effect within a given sex. For example, the relevance of the data from males in estimating the treatment effect for females depends on how similar the results from males are to the results from females and on how much data there are for females alone. Estimators of sex-specific treatment effects have greater precision than estimators based solely on the data for a given sex (Pennello 2018). As noted earlier, sex is only one of many factors for which subgroup

[47] See the guidance for industry *Multiple Endpoints in Clinical Trials* (October 2022).

analyses are typically performed, such that subgroup estimated treatment effects are subject to random highs and lows, being far above or far below the respective underlying subgroup treatment effect. Prespecified statistical approaches, which can also simultaneously consider multiple factors, should quantitatively address these random highs and lows and can reduce the potential for misinterpretation and making incorrect decisions resulting from those misinterpretations (Lipsky 2010).

D. Reporting Results of Analyses

As mentioned in section II.B of this guidance, sponsors must include in their annual reports for drug and biological products conducted under an IND, the number of participants entered into the study to date tabulated by "age group, gender, and race," and sponsors must present safety and effectiveness data in the clinical data section of an NDA by "gender, age, and racial subgroups."[48] Because the enrollment demographics of the clinical study may impact the generalizability of the conclusions, for clinical studies of devices, FDA recommends that sponsors report the number and proportion of study participants by sex, and gender[49] as appropriate, who were treated or diagnosed with the device as part of a clinical study as appropriate. Where statistical significance is achieved for an average treatment effect for the overall population, the results for each subgroup by sex should be examined to understand whether the finding for the overall population was driven by the results in only one of the sexes. Any potential difference by sex should be investigated, explained, and discussed with the Agency.

The clinical significance of the difference in observed treatment effects between females and males should be considered. As sex may be associated with other factors (e.g., weight) that influence the size of the treatment effect, sponsors should collect and evaluate data in the trial or study on any factors that may impact the treatment effect's size or contribute to differences in treatment effect, including analysis of those factors that may confound or contribute to an observed difference in treatment effect by sex. An assessment should also be made on any other important differences by sex, such as adherence to the assigned treatment (see Venditti 2023). Results from the evaluation of sex differences may help inform product labeling, which may include the findings of PK differences for females and males to help inform treatment decisions.

E. Considerations if Differences in Treatment Effects Between Females and Males Are Anticipated at the Design Stage

If important differences in the treatment effect by sex are anticipated at the trial design stage, sponsors should enroll an adequate number of participants from each sex to conduct an informative benefit-risk assessment. Sponsors should prespecify statistical analyses for evaluating and reporting differences in treatment effects between females and males.

[48] 21 CFR 312.33(a)(2) and 314.50(d)(5)(v) through (vi). While the Demographic Rule uses the term *gender* when referring to sex, this guidance uses the term *sex* as defined in section II.A of this guidance.

[49] For more information on the reporting of sex- and gender-specific data, please see the draft guidance for industry and FDA staff *Evaluation of Sex-Specific and Gender-Specific Data in Medical Device Clinical Studies*.

When a clinically important treatment effect is more likely for one sex than another sex, an early-phase trial (e.g., phase 1/phase 2) should ideally be performed to obtain information on differences by sex. If there is evidence from the early-phase trials of benefit for a particular sex and uncertainty around benefit for another sex, pivotal trials[50] can be designed to establish benefit for the sex for which there is evidence of benefit and also continue to study the effects of the product for the sex in which there is uncertainty around the benefit.

In such a setting where there is biological plausibility for benefit in a given sex and uncertainty around benefit for another sex, a trial can include certain approaches to control the Type I error probability across testing in the overall population and testing separately within a given sex. Such testing schemes are used due to concerns that adding data from the sex for which there is large uncertainty around benefit to the data from the sex for which there is expectation of benefit will reduce the probability of a statistically significant finding. With such an approach, if statistical significance is achieved only for the sex where there was expectation of benefit, then performing a statistical test after adding the data from another sex will only be capable of determining whether there is evidence of an average treatment effect in the overall population. The test in the overall population may be driven by results in the sex where benefit was expected and does not identify a treatment effect within the sex for which there was uncertainty around benefit. The estimated treatment effect and the estimated treatment effect's reliability would need to be considered before determining whether there is benefit for the sex for which benefit was uncertain.

V. NONCLINICAL CONSIDERATIONS

To support clinical testing of an investigational drug as part of an IND, sponsors are required to provide to FDA the pharmacology and toxicology data on which the sponsor has concluded that the proposed clinical investigation is reasonably safe to conduct.[51] These data typically include toxicology assessments conducted in animals.[52] Similarly, information on nonclinical laboratory studies may be submitted in an investigational device exemption application.[53] It is generally

[50] For more information on pivotal clinical investigations for medical devices, please see the guidance for industry, clinical investigators, institutional review boards, and FDA staff *Design Considerations for Pivotal Clinical Investigations for Medical Devices* (November 2013). See also the guidances for industry and FDA staff *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* (August 2019) and *Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions* (August 2019).

[51] 21 CFR 312.23(a)(8).

[52] FDA supports reducing, refining, and replacing animal use in testing when feasible. We encourage sponsors to consult with FDA if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. Sponsors should consider whether any such nonanimal testing method or approach would permit the identification of any sex-based differences in toxicity or other safety assessments. We will consider if such an alternative method is sufficient to meet the regulatory need.

[53] 21 CFR 812.20(b)(2) and 812.27(b)(3). For guidance on the types of nonclinical studies recommended, including their timing relative to clinical development, see the ICH guidances for industry *M3(R2) Nonclinical Safety Studies*

recommended that nonclinical toxicology drug and device studies that are conducted via animal testing use adequate numbers of male and female animals to permit the identification of any sex-based differences in toxicity or other safety assessments. These animal studies can be used to safeguard human research participants by inferring safety in humans based on the results. It may be appropriate in some circumstances, for example, when a disease or condition usually manifests in a single sex (e.g., menopause, diseases with X-linked recessive inheritance), to limit the nonclinical assessment to a single sex.

VI. OTHER GENERAL CONSIDERATIONS

- Where evidence collected during clinical development identifies potential sex differences, such differences should be explored as much as possible in clinical trials to support a marketing application for a product and, if appropriately justified, may potentially be further explored in a study after approval.[54]

- FDA can require a postmarketing study when applicable criteria are met, including to assess a known serious risk, signals of a serious risk, or to identify an unexpected serious risk when data indicate the potential for a serious risk, including for individuals who are pregnant or lactating.[55]

- When clinically significant differences in safety or effectiveness between females and males are detected, the applicant should propose how to address those differences (e.g., different recommended dosage in females and males, more frequent monitoring in one sex) in their marketing application.

- Postmarket studies and surveillance efforts should note whether safety signals differ by sex; these differences could lead to further investigation.

for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010); *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012); and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010). Additional information regarding medical device nonclinical studies is available in the guidance for industry and FDA staff *General Considerations for Animal Studies Intended to Evaluate Medical Devices* (March 2023).

[54] For more information on postmarketing commitments and postmarket surveillance, see the guidances for industry *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (February 2006) and *Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act* (October 2022).

[55] See footnote 41. For drugs, see section 505(o)(3) of FD&C Act. See also the draft guidances for industry *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and *Postapproval Pregnancy Safety Studies*. For devices, see the guidances for industry and FDA staff *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval*. Also for devices, see the guidance for industry and FDA staff *Procedures for Handling Post-Approval Studies Imposed by Premarket Approval Application Order* (October 2022).

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