

## **Biologic Variability to Drug Response: Sex Differences in Clinical Trials**

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### **Meeting Summary**

#### **Introduction**

Individuals can have different responses to the same drug, and in some cases biologic variability can lead to unpredictable adverse events that may not have been observed during clinical trials. Understanding the extent to which specific intrinsic and extrinsic factors help explain varying responses is increasingly becoming the focus of medical product development. One factor that may affect the safety and efficacy of a drug is the patient's sex. Pharmacokinetic differences in rates of metabolism, absorption, and excretion of a given substance, for example, can have an impact on how members of each sex respond to a drug. When variability in response between men and women is observed during clinical trials, it is not clear what these differences mean or when they might be clinically meaningful. Randomized controlled trials (RCTs) have long been considered the "gold standard" for measuring safety and efficacy, but traditional population-mean-based RCTs do not always provide insight into the differential responses of every subgroup (or of a given individual). To better ensure the safety and efficacy of drugs and biologics, it will be important to improve our understanding of the causes of variability in drug response, when it should be measured, and how best to design clinical trials to capture it.

#### **Biologic Variability in Drug Response**

It is well-known that individuals can vary widely in their responses to the same medication. A treatment that has been shown to be safe and effective in a particular population may have no effect—or can cause adverse effects—in certain individuals or subpopulations. Biologic variability in drug response can be linked to numerous, sometimes overlapping factors, including genetic differences, factors such as race, age, and sex, and environmental and/or behavioral factors such as alcohol use, climate, and diet. The cumulative effect of this variability is significant. Adverse drug reactions alone result in more than 100,000 deaths and cost the US health system between \$30 and \$130 billion per year.<sup>1</sup>

Accurately predicting and addressing the effects of biologic variability during drug development is a source of growing concern for researchers, drug sponsors, and regulators.<sup>2</sup> These challenges include insufficient understanding of the sources of biologic variability, underrepresentation of certain demographic groups (such as women and minorities) in some clinical trials, and the challenges of designing and conducting clinical trials that are able to capture meaningful data on that variability.<sup>3</sup> Achieving a better understanding of how and when biologic variability happens—as well as when the effect of that variability on patients is clinically significant—is necessary to ensure public health and safety and to improve clinical outcomes.

Sex is perhaps the most well-documented factor linked to variations in drug pharmacokinetics (PK) (i.e., absorption, distribution, metabolism, and excretion of a drug) and/or pharmacodynamics (PD) (i.e., the way in which a drug affects the body).<sup>4,5,6,7</sup> However, the underlying reasons for sex-linked variability in drug response are not fully understood, in part because women have historically been underrepresented or excluded from some clinical trials. This was due to a range of issues, including concerns over safety risks for women who may become pregnant and reluctance by researchers to address the

complex interactions of female hormones and drug compounds.<sup>8</sup> During the 1980s, as scientific evidence of significant differences in the ways drugs affected men and women emerged, the medical research community became increasingly aware that preventing or discouraging women from participating in clinical trials was limiting the ability to fully investigate those differences, with negative consequences for women's health.<sup>9,10</sup> Although women's participation in clinical trials has markedly improved since that time, barriers to recruitment and retention persist.

## Current Regulatory Requirements and Approaches to Addressing Biologic Variability in Drug Response

Drug sponsors are required to report demographic data (age, race/ethnicity, gender) and to conduct subgroup analysis for safety and efficacy in applications for regulatory approval. Yet there are currently no statutory or regulatory requirements for sponsors to include specific subgroups as participants in clinical trials.<sup>11</sup> Over the past two decades, the U.S. Food and Drug Administration (FDA) has taken steps to encourage greater representation of certain subgroups in trials submitted for regulatory review, and has issued several guidances for industry regarding specific populations, including pediatric, elderly, and female patients.<sup>12,13,14</sup>

There have also been parallel efforts to ensure adequate subgroup inclusion in NIH-funded research. In 1993, Congress passed the NIH Revitalization Act, which required NIH-funded investigators to include women and minorities in all of its clinical research studies, and stipulated that Phase III clinical trials must include women and minorities in numbers that would allow for valid analyses of differences in intervention effect.<sup>15</sup> In October 2015, the Government Accountability Office released a report regarding the state of women's participation in NIH-funded clinical research. While the investigation found that women represented 60 percent of NIH-funded phase III clinical trial participants, it also found that NIH did not routinely examine detailed enrollment data, which limited its ability to ensure that women were adequately enrolled across specific disease areas.<sup>16</sup> The report also noted that NIH does not have the ability to easily collect and report summary data on whether grantees are including sex-specific analyses in their phase III trial plans.<sup>17</sup> NIH has recognized that preclinical researchers continue to favor male animal subjects or omit information on the sex of the study animals entirely, which can undermine the rigor and validity of preclinical study design.<sup>18</sup> In order to correct this imbalance and improve the knowledge base about the effect of sex as a biological variable in clinical research, NIH implemented a revised policy in January 2016 to require the consideration of sex as a biological variable in preclinical applications.<sup>19</sup>

### The Food and Drug Administration Safety and Innovation Act of 2012

The Food and Drug Safety and Innovation Act of 2012 (FDASIA) directed FDA to examine how well demographic subgroups are included in clinical trials, as well as how readily demographic subgroup data are available in applications for drugs, biologics, and medical devices submitted for approval.<sup>20</sup> In its review, the FDA reported that in general, demographic profiles of clinical trial participants were included in applications submitted for approval, and the majority of applications contained subgroup analysis of treatment effects. At the same time, racial minority subgroups were underrepresented in clinical trials. An analysis of more recent data confirmed FDA's findings, underscoring the need for greater representation of racial minorities in clinical research.<sup>21</sup>

The agency's report also noted that participation in clinical trials by subgroup populations does not guarantee that sufficient data were collected in order to conduct credible subgroup analysis or to adequately detect differences in treatment effect between subgroups.<sup>22</sup> Section 907 also directed the

Agency to produce an action plan based on this review. Released in 2014, the final action plan contained 27 recommendations to 1) improve the completeness and quality of the demographic subgroup data contained within medical product applications; 2) identify barriers to enrolling members of demographic subgroups into clinical trials and utilize strategies to address those barriers; and 3) make demographic subgroup data more readily available to the public.<sup>23</sup>

Since 2014, FDA has taken key steps to implement the action plan. The agency has developed a plan to support research aimed at increasing understanding of clinical outcomes across different racial subgroups, and FDA's Office of Women's Health has released a roadmap that provides strategies for conducting research to improve women's health.<sup>24,25</sup> The agency has also established a working group focused on implementing communication strategies for populations that are under-represented in clinical trials.<sup>26</sup> FDA's Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health (CDRH) have made modifications to their clinical review templates to encourage reviewers to give more consideration to subgroup data and analysis.<sup>27</sup> CDRH has also developed guidance regarding the evaluation of sex-specific data in clinical studies for medical devices, and CDER now provides Drug Trials Snapshots for every new molecular entity approved since January 2015.<sup>28</sup> These Snapshots are part of an effort to not only increase transparency, but catalyze a broader scientific discussion around variability in drug response by providing information on who participated in the pivotal trials used to approve the drug, stratified by sex, race, and age. Any known differences in benefits or side effects of the drug are also stratified by these categories.<sup>29</sup>

#### Leveraging New Drug Development Tools and Trial Design Approaches

Despite growing understanding of how factors like sex, race, age and environment can influence drug response, drug development still largely follows a population-mean-driven, "one size fits all" approach. Even in the emerging field of precision medicine, which harnesses advancements in biomarker science and pharmacogenomics to develop more targeted therapies, many efforts are disease-focused and driven by specific variations in genetic sequences, rather than the complex, multifactorial processes that influence a person's health.<sup>30</sup> In order for the field of precision medicine to deliver fully on its vision, there is a need to consider new approaches to drug development and regulation. Recent scientific and technological advances in the fields of clinical pharmacology and pharmacogenomics offer substantial promise in supporting the development of such approaches.

Innovative trial designs may also offer advantages in identifying and understanding subgroup variability. Though randomized controlled trials (RCTs) have long been the most reliable method for determining the true effect of a given treatment, the strict parameters that govern the methodology of RCTs may limit such a trial's usefulness in certain contexts.<sup>31</sup> RCTs are often not sufficiently powered to establish differences between subgroups, which makes the resulting findings of subgroup analysis questionable.<sup>32,33</sup> Given these limitations, it may be necessary to consider alternative research strategies that may be better suited to capturing biologic variability in a manner that can support both regulatory and clinical decision-making. Possible approaches include the broader application of Bayesian statistical methods, N-of-1 trials (also known as single-patient trials), and the use of data from additional sources to supplement the results of RCTs.

#### Workshop Objectives

The Duke-Margolis Center for Health Policy, in partnership with FDA, convened an expert workshop on May 16<sup>th</sup>, 2016 to: 1) discuss the potential sources of biologic variability, including sex differences, that

may have an impact on the safety and efficacy of FDA-approved drugs and biologics; 2) explore the current methods for detecting and determining the significance of subgroup variation—and sex-based differences in particular—in clinical trials; and 3) identify and discuss viable research strategies that may be useful in capturing meaningful sex differences or other sources of variability in drug response. This workshop provided an opportunity for a broad set of representatives from across academia, industry, government, and other stakeholder groups to engage in discussion and identify potential solutions to the barriers that have hindered the ability to understand and address biologic variability in drug response.

### Methods for Identifying Meaningful Subgroup Variation

Though subgroup variability in drug response is common, it is not always clear when those differences are clinically significant, particularly in early stages of drug development. Participants began the day by discussing a broad range of factors that can influence drug response, including: sex, age, race/ethnicity, body habitus, the makeup of an individual’s microbiome, drug-drug and drug-diet interactions, the timing of dosing, genomic variation, and off-target effects (in which a drug interacts or binds with a protein other than its target, or otherwise causes some unintended effect). Participants also suggested that disease severity be included as another potential subgroup for analysis.

Participants also discussed the issue of confounding. Many of the factors under discussion, particularly age, sex, and body habitus, are challenging to study individually because they can all affect each other. Therefore, it may be necessary to focus on the interrelationships between these factors to fully understand the causes and mechanisms of variability, considering subgroups as co-variables rather than attempting to isolate one variable.

Several participants suggested that examining subgroups may eventually cease to be a useful analytical approach, particularly as the fields of precision medicine and pharmacogenomics evolve. Race and ethnicity, for example, are often used as proxies for some other factor that is the true cause of variability, but that may not be well understood. Similarly, biologic sex may be a proxy for other differences between men and women, such as general body size. It was emphasized that identifying true biologic variability relies on understanding the underlying mechanisms that lead to a particular outcome.

Participants noted that recent advances in the collection and analysis of genomic data have been helpful in uncovering the mechanisms behind biologic variability, but cautioned that even comprehensive genomic data may not provide a full picture of what might be causing subgroup (or individual) variability. Participants also suggested that linking electronic health records with existing biobank data could be a useful way to uncover new disease pathways and identify how and why drugs might affect an individual a certain way. Additionally, human phenomic science—in which phenotypic responses are observed and recorded for a small number of patients to identify the significance of molecular pathways

Key Potential Sources of Biologic Variability
<ul style="list-style-type: none"><li>• Sex</li><li>• Age</li><li>• Race/ethnicity</li><li>• Body habitus</li><li>• The makeup of an individual’s microbiome</li><li>• Drug-drug and drug-diet interactions</li><li>• Dose timing</li><li>• Genomic variation</li><li>• Disease severity</li><li>• Off-target effects</li></ul>

that may be involved in disease and drug response—may also be a resource for increasing our understanding of the sources of variability.

### Identifying Sex-Linked Differences in Response

Several participants questioned the classification of women as a subgroup, given that they make up more than 50 percent of the US population. It was also suggested that sex should be given more prominent consideration in clinical trial analysis, and should not be used as a secondary endpoint or secondary variable. Particularly in disease areas where there are well-known differences between men and women (such as cardiovascular disease and diabetes), it may be preferable for researchers to assume *a priori* that there is a difference between how men and women will respond to a drug until proven otherwise, rather than rely on the standard null hypothesis that assumes no difference.

Participants also discussed the use of forest plots to identify variability, as such visual displays can be helpful in comparing subgroup results. However, it was noted that the usefulness of this approach is limited by the nature of the trial population, which in some cases may be more homogeneous than the general disease population. Participants emphasized that epidemiological data is crucial in understanding baseline differences in the population being studied, which can in turn inform interpretation of variability. It was also noted that in some past cases, sex differences have not been detected in the PK data collected during clinical trials, but adverse events in women were reported after the drug has been approved. Participants suggested that it may be necessary to more closely examine PD data collected during clinical trials to better anticipate when adverse effects might vary by sex. Other participants pointed out that it would be useful to have more information on the role that sex hormones play in drug response, which is not currently well-understood.

### The Role of Clinical Pharmacology Tools

It was generally agreed that, where possible, pre-clinical and early clinical development tools should be applied to help sponsors identify potential variability in response as early as possible in the development process. It was suggested, for example, that data on age and sex be collected and analyzed in animal models to help predict the occurrence of variability in humans. However, some participants were skeptical of this proposal, as PK/PD data collected from animal models is challenging to extrapolate to humans. It was also noted that, while recent evidence has suggested pre-clinical studies have become much more likely to include information on sex, there has been little analysis of the impact that information may have on the later stages of trial design.

Participants agreed that although the PK and PD mechanisms that lead to variability are fairly well-understood, this knowledge is often used in trial design at the wrong time and is incorporated at too late a stage in drug development. It was suggested that FDA could help address this issue by requiring sponsors to use more of the body of knowledge behind PK and PD mechanisms during Phase IIB trials, which would in turn help to better inform Phase III trial design. Stakeholders also discussed the need to refine the scientific approach to measure certain differences in drug response throughout the development process, particularly for subjective outcomes such as pain reduction. More rigorous methods for capturing these outcomes will help to further understanding of when variability rises to the level of clinical significance.

While subgroup analysis from pivotal Phase III trials can be useful for generating hypotheses for future trials, it was acknowledged that they are not ideal mechanisms for understanding variability, as their purpose is to collect evidence for regulatory approval. Furthermore, it is unlikely that all sources of

variability will be identified prior to approval, regardless of the tools and methods applied in the pre-market setting. Post-marketing surveillance and follow-up studies will still be important mechanisms for identifying and understanding variability in response to particular drugs. Participants also noted that the field would benefit from a more systematic, comprehensive approach to understanding variability and its sources, rather than relying principally on anecdotal examinations of individual drugs and their differential impact.

### Incorporating Biologic Variability into the Drug Development Process

From a regulatory perspective, the ultimate goal with respect to biologic variability is to anticipate and account for meaningful differences, and to ensure the optimal use of drugs in specific patients or subsets of patients. There are currently several ways of accomplishing this goal, either through trial design strategies based on biological priors (e.g., restrictive entry trials or over-enrollment of particular subgroups) or through analytic strategies that evaluate variability in small, dedicated clinical studies (though it is rare to use either of these methods to identify sex differences). Sex is most commonly evaluated as a subgroup in a much larger population trial, although questions remain regarding what constitutes a meaningful difference in drug response between men and women and how best to interpret clinical trial data.

Participants cautioned that there can often be a presumption that sex is the most important subgroup variable, and that may not always be the case. Trials are largely designed to examine various groups of co-variables without knowing at the outset what the most important variable will be; and assuming sex will be the most critical variable may cause researchers to overlook other potential sources of variability. There was broad agreement from participants that adequately powering trials in order to capture subgroup effects like sex differences is a significant concern. Increasing the number of subgroups to be examined in a trial also increases the amount of people, time, and money necessary to complete the study, and these increased costs can become prohibitive.

### Harnessing Innovative Trial Design Strategies

Participants broadly agreed that there is a need for more focused and creative trial design to help tackle some of the issues regarding both sex differences in drug response and biologic variability generally. Several specific alternative trial design and statistical analysis methods to capture and analyze sex differences during the drug development process were discussed. Some participants suggested that the use of Bayesian statistical methods can help defray some of the costs associated with traditional trials. Unlike classical, “frequentist” approaches to statistical analysis, Bayesian analysis allows for the incorporation of prior knowledge into the statistical model, rather than relying solely on the data collected during the study. This approach offers several theoretical and practical advantages in the context of drug development. In particular, Bayesian approaches do not require the large, expensive-to-recruit trial populations that are necessary for conducting subgroup analysis under traditional frequentist approaches.

Another proposed statistical method involved “borrowing” information from the male subset of a trial and applying it to the female subset. It was suggested that this approach might best be applied in situations where the trial recruitment results insufficient numbers of female subjects to analyze separately. This approach would allow researchers to use baseline co-variables as a surrogate for sex (these can include things like age, body surface area, heart rate, etc.), and assumes that if enough of these genetic factors or biomarkers are collected from male patients, the amount of variation in the drug response in women can be predicted based on this supplementary data. This method also has the

potential to be used in other contexts, such as estimating differences in drug response across geographic regions in global trials.

Several participants expressed skepticism regarding the use of this kind of statistical borrowing technique. Participants emphasized that there is no shortage of women with diseases and that instead of using statistical methods to substitute data from men, researchers could directly study women. Some participants also expressed skepticism that this borrowing method could adequately illuminate the biological mechanisms behind any detected sex differences or other variations among subgroups. Participants emphasized that it is imperative that we understand the mechanisms and physiology behind these differences and that if the basic physiology of the condition is different between men and women, a drug's safety and efficacy cannot be assessed in women by borrowing data from men.

Other proposed trial design alternatives included using a frequentist approach that combines data from multiple studies to estimate a drug's effect on women. Participants suggested that it might also be possible to similarly combine data from all drugs across the same drug class to estimate class-wide effect differences in drug response. The use of cross-design synthesis—in which evidence from observational and experimental randomized controlled trials is integrated—was suggested as another potential design alternative. A number of participants mentioned additional sources of information that could be incorporated into trial design or be used in subgroup analysis, including data from electronic health records and biobanks.

### Improving Communication and Recruitment for Clinical Trials

Participants also discussed the need not only to examine the design of clinical trials, but also barriers to recruiting and retaining women in clinical trials. In addition to pursuing higher education, owning businesses, and having careers, women are more likely to be the primary caretakers of children. This makes it even more difficult to enroll them in a clinical trial, even when they are aware that they are eligible. Participants also noted that it can be difficult to know where to go to find and recruit the kinds of women needed for a particular trial. Many participants agreed that more guidance and reporting on how to lower these barriers could help ensure enough women are enrolled in clinical trials. One participant also suggested that increasing the number of female principal investigators working on clinical trials might help to address some of the challenges to female trial recruitment.

The agency also elaborated on the role of Drug Trial Snapshots and how they can serve as a mechanism for making clinical trial data more readily available and transparent. Participants indicated that it's not clear who is currently using and benefiting from the Snapshots, though pharmaceutical manufacturers are quite interested in the information. Stakeholders suggested that Drug Trial Snapshots should be made standard and done for all new drug approvals.

### Next Steps

Participants identified several potential next steps. It was suggested that FDA collaborate with key stakeholders to develop a framework for leveraging early-stage development evidence to guide decisions on subgroup inclusion and analysis in clinical development plans. Stakeholders also suggested that it could be useful to standardize definitions for different age groups, as well as for terms such as "elderly." Other participants mentioned that FDA should encourage more use of modeling and simulation tools (also referred to as model-informed drug development), which could help to improve understanding of drug exposure and response in the drug development and review process.

There is also a need to increase awareness among women regarding their eligibility for clinical trials; participants noted that women are typically more likely to encourage their male partners and children to take part in trials, but are less likely to enroll in a trial themselves. There was also significant interest from many participants in expanding the content of FDA's Drug Trial Snapshots to include information regarding any observed sex differences or other subgroup differences. This information could include details on whether subgroup analysis results (if available) were statistically significant, as well as caveats regarding how adequately the trial was powered, and what effects that might have on subgroup analysis results. Additionally, participants suggested that it could be useful to begin updating the Drug Trial Snapshots on a regular basis, drawing information from subsequent drug studies, electronic health records of patients utilizing the drug, or other sources in order to provide information on reported rates of adverse events. Such data could also be stratified by subgroup to show whether a particular group suffers from increased rates of adverse events compared to other groups.

### Major Takeaways and Recommendations

- Confounding is a significant concern when assessing variation in drug response. Therefore, it may be necessary to focus on the interrelationships between these factors, considering subgroups as co-variables rather than attempting to isolate one variable.
- Researchers and sponsors need better strategies for understanding disease pathways and identifying biologic variability in drug response. New tools and approaches (e.g., linking of electronic health records with existing biobank data, application of human phenomic science) may be a resource for increasing understanding of the sources of variability.
- Women should be given more prominent consideration in clinical trial analysis, and should not be used as a secondary endpoint or secondary variable. Particularly in disease areas where there are well-known sex-linked differences in drug response, it may be preferable for researchers to assume this *a priori*.
- FDA could consider requiring sponsors to use more of the body of knowledge behind PK and PD mechanisms during Phase IIB trials, which would in turn help to better inform Phase III trial design.
- FDA could also collaborate with key stakeholders to develop a framework for leveraging early-stage development evidence to guide decisions on subgroup inclusion and analysis in clinical development plans.
- Adequately powering trials to capture subgroup effects is a significant challenge, as increases in trial size lead to higher costs and longer trials. The application of newer statistical models, such as Bayesian analysis, could help to address some of these challenges.
- It will be important not only to examine the design of clinical trials but also barriers to recruiting and retaining women in clinical trials, as these broader challenges have not been fully addressed.
- FDA could consider making Drug Trial Snapshots a more comprehensive resource, by including details on whether any subgroup analyses were statistically significant, caveats regarding how adequately the trial was powered, and what effects that might have on subgroup analysis results.

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