

FDA Report

FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

August 2014



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Message from Margaret A. Hamburg, M.D., Commissioner of Food and Drugs

One of the core tenets of rigorous biomedical research, as well as a guiding principle of the FDA's goal to meet the health needs of patients across the demographic spectrum, is the importance of encouraging diversity in clinical trials.

When a more diverse population participates in clinical trials, we increase the potential to know more about the extent to which different subgroups—males and females, young and old, people of various racial and ethnic backgrounds, and patients with differing comorbid diseases and conditions—might respond to a medical product. And when subgroup data are analyzed, we have available more information about the product that can be communicated to the public. The result is greater assurance in the safety and effectiveness of the medical products used by a diverse population.

FDA has been addressing these issues since the 1980s, when we first released guidance about the importance of studying the effects of drugs in elderly patients. In the 1990s, we issued a "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" and established the Office of Women's Health. As a result, women today are far more adequately represented in the majority of clinical trials that are the basis for safety and effectiveness decisions about FDA-approved products. Moreover, analysis for sex differences in clinical drug trials, required by regulation since 1998, is now routinely done in new drug applications. More recently, we've been looking at ways to encourage greater inclusion of women in medical device trials. In 2011, we issued draft guidance outlining our expectations for sex-specific data analysis and reporting of medical device clinical study information, as well as recommending strategies for enrollment of women in clinical studies, and we have now issued a final version of that guidance.

Advances in science are also playing an increasingly important role in deepening our understanding of how patients within various subgroups respond to medical products. For example, information from areas such as pharmacogenomics is now being incorporated into product development and regulatory review to further address subgroup characteristics and population needs, helping to overcome the challenges of the "one-size-fits all" model of patient treatment. Ultimately, this is steering us towards the goal of tailoring treatments to individuals or subgroups of patients through personalized medicine—including patients in underserved and underrepresented populations.

But for all the progress we have made, there are still areas of concern, particularly involving underrepresentation of racial and ethnic minorities. That's why it was important that in 2010, as part of the Affordable Care Act, we were able to establish FDA's Office of Minority Health to advise FDA on ways to reduce health disparities among racial and ethnic subgroups.

In Section 907 of the 2012 Food and Drug Administration Safety and Innovation Act, Congress directed us to take a closer look at the inclusion and analysis of demographic subgroups in applications for drugs, biologics and devices—including by sex, race and ethnicity, and age—and report on our findings. A cross-agency task force analyzed 72 applications for drugs, biologics and devices approved in 2011. Our report, published in August

2013, found that the agency's statutes, regulations and policies generally give product sponsors a solid framework for providing data in their applications on the inclusion and analysis of demographic subgroups; in general, sponsors describe the demographic profiles of their clinical trial participants; and the majority of applications submitted to FDA include demographic subset analyses that the FDA shares with the public in a variety of ways.

But in that report, we also concluded that we could do better, and Section 907 gave us a vehicle for considering improvements. It directed that one year after the issuance of the Section 907 report we publish and provide to Congress an action plan outlining "recommendations for improving the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling; on the inclusion of such data, or the lack of availability of such data, in labeling; and on improving the public availability of such data to patients, health care providers, and researchers."

Today, after extensive consultation with stakeholders, FDA is delivering its *Action Plan to Enhance the Collection and Availability of Subgroup Data*. It includes 27 responsive and pragmatic actions, which are divided into three overarching priorities: improving the completeness and quality of demographic subgroup data collection, reporting and analysis (quality); identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation (participation); and making demographic subgroup data more available and transparent (transparency).

Some of the action items can be accomplished quickly while others will take longer to achieve and require additional resources. But once the plan is put fully in effect, I believe it will provide additional information to help health care providers and patients make decisions about the medical products they use.

Addressing the three priorities of quality, participation and transparency will require a multifaceted approach and the active participation of both FDA and our many stakeholders. We look forward to working with them as we implement this action plan.

Sincerely,

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data

Introduction and Background

Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)¹ directed the Food and Drug Administration (FDA or the Agency) to publish and provide to Congress a report “addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups, including sex, age, race, and ethnicity, is included in applications submitted to the Food and Drug Administration.” Section 907 also directed FDA to publish and provide to Congress an action plan outlining “recommendations for improving the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling; on the inclusion of such data, or the lack of availability of such data, in labeling; and on improving the public availability of such data to patients, health care providers, and researchers” and to indicate the applicability of these recommendations to the types of medical products addressed in Section 907. Congress also directed that the action plan be issued one year after the publication of the Section 907 report.

To fulfill these directives, an FDA-wide working group with representatives from the FDA’s Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Office of Commissioner undertook a detailed assessment of 72 applications for drugs, biologics and medical devices approved in 2011. In August 2013, FDA issued a report on the group’s findings, *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*.² The report concluded that the statutes, regulations and policies currently in place generally give sponsors a solid framework for providing data on the inclusion and analysis of demographic subgroups in their product applications and that FDA communicates this information in a variety of ways. It also concluded that the extent to which demographic subset data were analyzed varied across medical product types (drugs, biologics and medical devices) because of differences in regulatory requirements (drugs and biologic applications must, by regulation, include demographic subgroup analyses of effectiveness and safety). All of the biologics and drug applications included in FDA’s assessment and a majority of the medical device applications provided the composition of clinical study participants by age, race and sex. Participants’ sex was the most consistently reported in the medical product applications. For approved drugs and biologics, the extent to which patients were represented in clinical trials by age and sex tended to reflect the disease indication studied. For devices, patient participation by age and sex varied by product type. Ethnicity (as defined by the Office of Management

¹ Food and Drug Administration Safety and Innovation Act of 2012, P.L. 112-144, July 9, 2012.

² FDA Report. *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*. <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf>.

Neither the Section 907 report nor this action plan address pediatric age groups as this is largely addressed in Sections 501-511 of FDASIA and is subject to separate reporting.

and Budget data standards as “Hispanic or Latino” and “Not Hispanic or Latino”) was not consistently reported in clinical studies across medical product types. The report noted that including participants from different subgroups in clinical trials did not necessarily mean that sufficient data are collected on those subgroups for meaningful analysis or to allow detection of relevant subgroup differences.

As we³ began developing the action plan, we felt it was crucial to reach out to our stakeholders to hear their perspective, identify any concerns and listen to their recommendations about demographic subgroup representation, outcome analysis and public communications around this topic. Consequently, we opened a public docket from August 20, 2013, until May 16, 2014; held a public hearing on April 1, 2014; and had many other small group meetings with stakeholders.

Among the comments we heard:

- Some **patient advocacy groups** and **health professional groups** believe that the proportion of women, minorities and elderly patients in industry-sponsored clinical trials is not consistent with the prevalence of the disease in the underlying population. Some patient advocacy groups said that they believe health professionals and patients do not have sufficient demographic information to make well-informed treatment and diagnostic decisions. It was also noted that achieving racial and ethnic participation and relevance to U.S. subgroups can be a particular problem when foreign data is used.
- Some **industry representatives** said they believe there is a general lack of awareness about, and limited physical access to, clinical trials among some demographic subgroups. They also stated that in today’s global medical product market they sometimes conduct clinical trials in geographic regions with a racial and ethnic representation that is substantially different from the U.S. population.

The public comments and our many interactions with stakeholders made it very clear that FDA shares a common goal with patients, health professionals, researchers and the biomedical industry: **safe and effective medical products must be available to the broad range of patients who need them.** When participants in a clinical trial for a medical product reflect a diverse, real-world population (males and females, young and old, various racial and ethnic backgrounds, and patients with differing comorbid diseases and conditions) and when the subgroup data from the trial are appropriately analyzed, much more information can be known about the product and more meaningful clinical data can be communicated to the public.

With all of this in mind, FDA developed an action plan that we believe is both responsive and pragmatic, and, most critically, has the potential to contribute to the health of the American public. The plan is divided into three overarching priorities—quality, participation and transparency.

Priority One: Improve the completeness and quality of demographic subgroup data collection, reporting and analysis (**Quality**).

Priority Two: Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation (**Participation**).

Priority Three: Make demographic subgroup data more available and transparent (**Transparency**).

³ Throughout this report, the use of the word “we” refers to FDA as a whole. Action items that refer to “we” will be addressed across centers and offices.

What follows is a list of 27 specific actions divided up within the three priorities that FDA plans to implement, along with a projected timeframe for completion: short-term (within one year), intermediate-term (within 1 to 3 years) or long-term (within 3 to 5 years). Many of these actions will have a broad impact on the work of FDA's medical product centers and will require thoughtful implementation based on current evidence and available resources.

FDA's Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data reflects the Agency's commitment to encouraging the inclusion of a diverse patient population (with reference to sex, age, race and ethnicity) in biomedical research that supports applications for FDA-regulated medical products. Increasing representation is a multifaceted challenge that requires a multifaceted approach and the collaboration of our federal partners, industry, health care providers, patients and patient advocacy groups, academicians and community groups.

A consistent and recurring comment from all of our stakeholders was the desire to continue a dialogue with FDA on this important topic. We share that desire. Thus, we are reopening a docket to solicit public comments on the action plan and will plan additional opportunities for the members of the public to provide their input on various action items in the plan. Updates and progress on the action items will be posted to the Section 907 Web page on FDA's Web site, FDA.gov, on a regular basis.

FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data

The actions we are taking can be grouped into three main areas of emphasis and align with the mandate provided by Congress. Our actions seek to:

- 1) Improve the completeness and quality of demographic subgroup data collection, reporting and analysis (**Quality**);
- 2) Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation (**Participation**); and
- 3) Make demographic subgroup data more available and transparent (**Transparency**).

Some actions will help enhance the quality and consistency of the demographic data and analyses that sponsors submit to FDA. This enhanced quality and consistency will better enable identification of clinically meaningful knowledge gaps and differences across subgroups. Some actions are intended to remind sponsors to increase the diversity of clinical trial participants, taking into account the disease prevalence in demographic subgroups in the United States. Other actions involve FDA refining its policies and staff training to support more consistent and transparent collection, analysis and communication of demographic subgroup data across FDA review divisions. And finally, by engaging and communicating with the public, including with health professionals, about the importance of diversity in clinical research, we will encourage greater participation of diverse populations in clinical trials.

These actions may involve multiple approaches; may involve FDA staff alone; or may involve FDA in concert with other government stakeholders, research investigators and healthcare professionals, medical product industry sponsors and members of the public, including those in patient advocacy groups. The interactions within FDA and with external stakeholders are vital to successfully accomplish the common goals in this plan.

Each action outlined and detailed below also is captured in a summary chart (see Appendix A), which will be posted on FDA's Web site and updated as actions are completed.

Priority One: Improve the Completeness and Quality of Demographic Subgroup Data (Quality)

We plan to improve the completeness and quality of demographic subgroup data collection, reporting, and analysis by:

- 1.1. Reviewing and developing a work-plan for updating, and/or finalizing, relevant guidance on demographic subgroup data, including FDA staff training and outreach to external stakeholders, as needed, for implementation;**
- 1.2. Working with sponsors to revise medical product applications to enhance information on demographic subgroups in medical product applications;**
- 1.3. Strengthening FDA reviewer training by adding education/training around demographic inclusion, analysis, and communication of clinical data;**
- 1.4. Enhancing FDA's systems for collecting, analyzing, and communicating diverse clinical information to optimize safe and effective use of medical products in diverse populations over the total product life cycle; and,**

1.5. **Conducting research on specific areas of public health concern related to demographic subgroups.**

FDA's August 2013 report demonstrated that FDA's statutory and regulatory requirements, guidance documents, policies, and procedures generally inform sponsors and Agency staff about how demographic data should be collected and analyzed. Nevertheless, we intend to further enhance the quality and consistency of these efforts. It is important to provide industry with clear guidance about our expectations around the demographic data and analysis they submit. We will explore ways to standardize data fields so as to simplify the pooling of data across clinical studies and make it easier to identify trends regarding specific demographic subgroups or product areas.

1.1 **Reviewing and developing a work-plan for updating, and/or finalizing, relevant guidance on demographic subgroup data, including FDA staff training and outreach to external stakeholders, as needed, for implementation (*Short-term and intermediate-term completion goal*)**

FDA regulations and policies currently in place give product sponsors a solid framework for providing data in their applications on the inclusion and analysis of demographic subgroups studied. Nevertheless, we believe more improvements can be made.

Action Items:

- ✓ CDER and CBER plan to review—and update and/or finalize, as needed—relevant industry guidance and internal FDA good review practice documents to encourage greater demographic subgroup representation in clinical trials, subgroup analysis and communication of results. We welcome public input on new evidence or best practices that could inform revision of our existing guidance including:⁴
 - *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*
 - *Collection of Race and Ethnicity Data in Clinical Trials*
 - *ICH E7 Studies in Support of Special Populations: Geriatrics, both the original document and an amendment in 2012 with relevant questions and answers*⁵
- ✓ We plan to incorporate recommendations from the recent guidance *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* into reviewer templates, as appropriate, to provide staff training. We also plan to develop and offer an external webinar about how to use the guidance.

⁴ All FDA guidance discussed in this report can be accessed on FDA's web site at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>.

⁵ ICH is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, a collaboration of regulatory authorities and the pharmaceutical industry in Europe, Japan and the United States that discusses scientific and technical aspects of drug registration. More information is available at <http://www.ich.org>. ICH E-7 specifically urged inclusion of patients older than 75, a point not made in the original ICH guidance. The impact of this change would be anticipated in future years.

This guidance, finalized in August 2014, outlines FDA’s expectations and intent to improve the quality and consistency of available data on how well a medical device performs in both sexes. The final guidance includes recommendations on encouraging appropriate representation by sex in clinical studies of devices and explains that data from such studies should be appropriately analyzed by sex.

- ✓ We plan to begin drafting a guidance document on analysis and reporting of ethnicity, race and age in medical device clinical studies. In doing so, FDA plans to explore key barriers and limitations to meaningful data analysis.

1.2 Working with sponsors to revise medical product applications to enhance information on demographic subgroups in medical product applications (*Intermediate-term completion goal*)

FDA currently has frequent communications with sponsors during the product development process. These provide opportunities to remind sponsors to consider the diversity of target populations early in the development of their clinical trials and, later on, to consider whether subgroup diversity is represented in enrollment or conduct of multiple trials and at various time points throughout the product’s life cycle. A recent Good Review Practices (GRP) document, available to all CDER and CBER staff, pays particular attention to the need to examine study protocols for unwarranted exclusions (e.g., people over a certain age or with concomitant illnesses).

Different product centers have processes in place to communicate the importance of collecting information on diverse populations for specific indications and products. For example, in the case of medical devices, CDRH currently includes standard advisory language in investigational device exemption (IDE) letters that encourages sponsors to collect clinical trial data for racial and ethnic minorities in accordance with the 2005 FDA-wide final *Guidance on Collection of Race and Ethnicity Data in Clinical Trials* and to enroll patients who reflect the demographics of the affected population with regard to age, sex, race and ethnicity. The advisory language also recommends that in the study protocol sponsors provide contextual information to FDA on disease prevalence, diagnosis and treatment patterns, and plans to address any factors identified or suggested that could explain any potential for under-representation of women and minorities.

For drugs and biologics, current regulations require that, as part of the investigational new drug application (IND) process, annual reports be submitted to FDA that tabulate participants by sex, age and race. This provides an opportunity for review staff to monitor the adequacy of study-population diversity during product development and, together with the new Good Review Practice document, can serve as a basis for discussions about inclusion of diverse subgroups in clinical trials during the sponsor meetings that take place at various points in a company’s development program.

Action Item:

- ✓ CDER and CBER plan to revise the guidance on the Integrated Summary of Effectiveness (ISE) sections of new drug applications (NDA), and biologics license applications (BLA), with particular attention to the importance of demographic and other subgroup analyses. Consideration is also being given to developing guidance on the Integrated Summary of Safety (ISS).

The ISS and ISE sections are critical components of the clinical safety and efficacy portions of a marketing application and are based on integrated analyses, specifically including subgroup

analyses, of the data, once data collection is complete. The revised guidance should improve the quality of these analyses. When products are approved, the data in ISS and ISE sections, including subgroup data, can be reported to the public.

1.3 Strengthening FDA reviewer training by adding education/training around demographic inclusion, analysis, and communication of clinical data (*Intermediate-term completion goal*)

An integral and critical component of medical product development and FDA application review is our assessment of patient or population characteristics that may be relevant to the safety or effectiveness of the product. FDA reviewers—physicians, biomedical engineers, clinical pharmacologists, toxicologists, statisticians and other scientists—are constantly engaged with medical product sponsors throughout the life cycle of their products in evaluating these characteristics. During drug development, for example, beginning with initial animal studies and continuing with studies looking at pharmacokinetic data and effects in healthy populations, with studies in populations with the disease, and finally with the postmarket setting when a product is typically widely available for use by patients, we examine safety and effectiveness in the overall study population and in demographic subgroups. Each of these phases provides an opportunity for our review staff to discuss with sponsors the safety and effectiveness of their medical products in specific demographic groups.

Another training opportunity is available from FDA’s Office of Women’s Health (OWH), which jointly developed three continuing education courses on sex and gender differences with the NIH Office of Research on Women’s Health. The online series⁶ is free of charge and open to the public. Doctors, pharmacists and registered nurses, including FDA staffers, can receive continuing medical education credit for taking the course.

Action Items:

- ✓ We plan to require training for new clinical trial reviewers on the importance of demographic subgroup data inclusion, analysis and communication.
- ✓ We plan to offer additional education and training courses for experienced reviewers to better clarify FDA’s expectations for data collection and analysis related to demographic subgroups.

This provision of information will help ensure that FDA staff is knowledgeable and can consistently implement our policies and guidance in their interactions with sponsors and their review of subgroup data in applications.

1.4 Enhancing FDA’s systems for collecting, analyzing, and communicating diverse clinical information to optimize safe and effective use of medical products in diverse populations over the total product life cycle (*Intermediate-term to long-term completion goal*)

A pragmatic and effective solution for improving public availability of demographic data to patients, health care providers and researchers is to use a two-pronged approach that enables greater availability of diverse clinical evidence. Our approach would involve (1) identifying ways to better leverage existing clinical data and (2) strengthening systems to make better use of data that may be collected once medical products are available on

⁶ <https://sexandgendercourse.od.nih.gov/index.aspx>

the U.S. market. As resources become available, FDA would be able to enhance existing systems for collecting, analyzing, and communicating information to optimize safe and effective use of medical products in diverse populations.

We realized more clearly as we compiled the Section 907 report that additional clarification is needed about the collection of race and ethnicity data as recommended by FDA's guidance *Collection of Race and Ethnicity in Clinical Trials*. Stakeholders commented to the public docket that there are issues concerning the validity, both scientifically and clinically, of patient identification by race (phenotype) or ethnicity (a socio-cultural quality), rather than ancestry or genetic make-up, where appropriate.

Updating current thinking about standardized age categories (e.g., grouping older patients in more discrete categories for analysis (65 to 74 years old, or 75 to 84 years old, rather than younger than 65 years old or simply using birth year), was another recurring recommendation to both the docket and at public meetings. It was also specifically recommended in the 2012 Q & A addition to ICH E7.

Such updates in our current data collection procedures, including updating definitions of subgroups that may be clinically informative, can lead to more standardized data collection and can also enhance our understanding of clinical outcomes and trends in specific patient populations. To redefine these standards also requires updating the tools we use for data collection and analysis to hone our understanding on a more complex level. It has become increasingly important to have consistent approaches for collecting data for all medical product submissions.

Action Items:

- ✓ We plan to work, to the extent possible, towards better standardization of data collection categories for age, racial and ethnic groups in submitted applications to facilitate harmonized data collection and analysis of subgroup outcome trends.

Data standardization with regard to demographic subgroups is an important, yet difficult, issue to address, and one that FDA cannot tackle alone. We are prepared to work with stakeholders, such as the Clinical Data Interchange Standards Consortium (CDISC), advocacy groups, industry, our federal partners, and our international regulatory partners, in exploring how to approach data standardization and examining how this information can contribute to greater scientific and clinical knowledge about demographic subgroups. As those broader discussions occur, we are interested in moving forward to achieve greater consistency and standardization in current submissions of this demographic information, given available resources. Some of this work will be addressed as part of our review of guidance under Action Item 1.1.

- ✓ We plan to revise our MedWatch forms to enable a standardized collection of demographic information on possible adverse events that occur after medical products are broadly available on the U.S. market.

Because not all differences in safety or effectiveness for medical products can be anticipated or discovered during the premarket setting, it is vital to have robust postmarket surveillance systems in place. FDA's Adverse Event Reporting System (FAERS) collects information on drugs and biologics (except for vaccines); the Vaccine Adverse Event Reporting System (VAERS) collects information on vaccines, and the Medical Device Adverse Event Database (MAUDE) collects information on medical devices. CBER, CDER and CDRH are currently assessing these

systems for opportunities to improve demographic category standardization to make reporting more user-friendly for health professionals, patients and others. For example, race may be reported as free text instead of in limited drop-down categories on MedWatch forms used to report adverse events. The MedWatch form is currently going through re-review and reauthorization by the Office of Management and Budget. As part of that process, FDA plans to develop a more standardized approach.

- ✓ We plan to strengthen systems and infrastructure for making better use of data once products are broadly available on the U.S. market.

The Mini-Sentinel pilot⁷ is part of the Sentinel Initiative, launched in 2008. Mini-Sentinel is enabling FDA to work with partners who can access pre-existing electronic health care data from multiple data sources, including major health networks, to identify and better understand safety signals in 150 million people, including demographic subgroups, in response to queries FDA poses for analysis.

CDRH's proposed National Medical Device Postmarket Surveillance System is designed to meet the challenges of rapidly evolving medical devices, health care delivery and information technology. This is built on a variety of initiatives, including CDRH's Unique Device Identifier (UDI) Rule which will require that most devices carry a UDI, a unique numeric or alphanumeric code that identifies the product, its lot or batch, when it was made and its expiration date. When implemented and incorporated into registries, electronic health records, administrative claims data and other sources, it will increase the potential to gather information about a specific devices use in larger and typically more diverse patient populations. UDI implementation is a key component of a robust National Medical Device Postmarket Surveillance System, which we envision will enable quick identification of potential safety signals from a variety of privacy-protected sources, while reducing the burden and cost associated with surveillance as well as approval/clearance of new devices and existing devices for new uses or patient groups. The timeline for completion of the National System will depend on available resources.

1.5 Conducting research on specific areas of public health concern related to demographic subgroups (Ongoing and Intermediate-term completion goal)

FDA has implemented a variety of policy and programmatic improvements over the years to enhance the representation of relevant demographic subgroups in clinical trials and the analysis of subgroup data. We also have supported research on issues such as sex differences and health disparities that affect demographic subgroups.

For example, since 1994, OWH has funded more than 300 research projects examining sex differences in FDA-regulated products and diseases unique to, or predominantly experienced by, women. Information gleaned in these research projects has facilitated regulatory decision-making.⁸ OWH has also partnered with the NIH Office

⁷ For more on Mini-Sentinel, see <http://mini-sentinel.org/>.

⁸ For more on research support by FDA's Office of Women's Health, see FDA's web page at <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/default.htm>.

of Research on Women's Health to support research through the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health.⁹

More recently, FDA's Office of Minority Health (OMH), established in 2011, has funded research projects with FDA's medical product centers and with the University of Maryland and Georgetown Centers of Excellence in Regulatory Science and Innovation (CERSI).¹⁰ OMH also collaborates with the National Institutes of Health (National Institute of Minority Health and Health Disparities, the National Human Genome Research Institute and the National Cancer Institute Center for the Reduction of Cancer Health Disparities) and with established research projects at academic centers, all of which support advancing FDA's understanding of health disparities.

However, additional research is needed to better understand issues surrounding recruitment, participation and outcome analysis of demographic subgroup populations, focusing on certain disease areas where significant outcome differences may be anticipated.

Action Items:

- ✓ OWH plans to develop a new women's health research roadmap that will help to better coordinate research across the Agency and target OWH funding to projects that answer specific regulatory research questions and emerging priorities from the product review centers.
- ✓ OMH plans to develop research projects leading to better understanding of medical product clinical outcomes in racial/ethnic demographic subgroups. This work will serve to identify and address aspects of clinical trials in therapeutic areas impacted by low inclusion, ranging from participation to outcome analysis of demographic subgroup populations.
- ✓ OMH plans to collaborate with NIH's National Human Genome Research Institute in research into the role of genetics and genomics in health disparities. Findings from this collaboration are expected to clarify how the collection of data on race and ethnicity aligns with the evolving knowledge base for ancestry and genomics.
- ✓ As resources allow, we plan to develop a program of directed research in which FDA investigators could select a certain disease category and conduct an in-depth look at the data contained in relevant applications submitted over a specified time period (i.e., 5-10 years).

Some stakeholders have told us they believe some demographic subgroups don't respond as well to treatments for certain disease categories such as cardiovascular disease and diabetes. The assessment will be designed to examine the data for trends; identify the adequacy of demographic subgroup representation in trials; assess the content and quality of subgroup

⁹ <http://orwh.od.nih.gov/sexinscience/researchtrainingresources/scor.asp>

¹⁰ For more on FDA's OMH CERSI partnerships, see <http://www.cersi.umd.edu/research> and <http://regulatoryscience.georgetown.edu/cersi>

See also areas of research supported by the Office of Minority Health at <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm349115.htm>.

analyses for safety and effectiveness; and assess the adequacy of the analyses to determine potential differences in subgroups

FDA plans to share results of FDA-funded research publicly, as appropriate. This sharing of information is illustrated by the recently-published meta-analysis of sex differences in cardiac resynchronization therapy (CRT).¹¹

Priority Two: Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation (Participation)

We plan to identify barriers to subgroup participation in U.S.-based clinical trials and employ strategies to encourage greater participation by:

- 2.1 Seeking further clarity about barriers to subgroup participation rates;**
- 2.2 Implementing efforts to enhance appropriate use of enrollment criteria in clinical trial protocols;**
- 2.3 Collaborating with NIH, industry and other interested stakeholders to broaden diverse participation in clinical research; and,**
- 2.4 Using FDA’s communication channels to encourage clinical trial participation by demographic subgroups.**

Dialogue at the public hearing and past workshops along with FDA’s findings in the August 2013 report all highlight that certain subgroups in the United States are less likely to be enrolled in clinical trials than the population as a whole. This is particularly noticeable among Blacks, Hispanics, U.S. Asians, and patients over the age of 75.

Participation in clinical trials is voluntary, so in order to have clinical trials with diversity among participants, a diverse population of people has to be willing to participate. Many barriers to participation by underrepresented subgroups in the United States have been cited: limited numbers of investigators who can help enroll underrepresented subgroups or who have access to a broader range of patient subgroups; patients and families with negative attitudes about medical research and concerns about risk; patient inconvenience; availability of transportation; geographic location; and insurance status. Lower participation by those patients over the age of 75 is thought to reflect protocol exclusions. Observations since the 1980s have shown that, for most drugs, gender participation is appropriate to dosage.

With regard to balanced representation in clinical trials, we believe—and our own data demonstrate—that for approved drugs and biologics, the extent to which patients were represented in clinical trials by age and sex tended to reflect the disease indication studied, noting again the deficit of people over 75. For devices, patient participation by age and sex varied by product area. FDA fully supports efforts to encourage participation of underrepresented ethnic and racial subgroups participating in clinical trials in applications for all FDA-regulated medical products, so that knowledge about the safety and effectiveness of these products is informative to patients who may use the products.

¹¹ Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac Resynchronization Therapy in Women: US Food and Drug Administration Meta-analysis of Patient-Level Data. *JAMA Intern Med.* 2014;174(8):1340-1348. doi:10.1001/jamainternmed.2014.2717

Clearly, this is a multifaceted problem that requires a multifaceted approach. FDA is committed to encouraging clinical trial participation by diverse demographic subgroups. FDA will need to work in concert with the National Institutes of Health (NIH), advocacy groups, and industry to raise awareness and identify best practices for how to improve the inclusion of demographic subgroups in biomedical research.

2.1 Seeking further clarity about barriers to subgroup participation rates (*Short-term completion goal*)

FDA has sought to better understand potential barriers to participation in clinical trials. Last year, FDA's OMH funded a study with the University of Maryland's Center of Excellence in Regulatory Science and Innovation (CERSI) that surveyed researchers both in and out of FDA. Researchers found that although minorities may be less likely to participate in FDA-regulated research, the issue is not one of race and ethnicity alone. A myriad of other factors influence an individual's likelihood of participating in FDA-regulated research, including access to trials and healthcare, both of which may be largely driven by socioeconomic status; the disease being studied; and the research design. Surveys such as this can be used to educate and engage researchers.

Action Item:

- ✓ Working with the Institute of Medicine, OMH plans to convene a meeting of experts in 2015 to better understand contemporary barriers to participation by minorities in clinical trials.

OMH plans to collaborate with the Department of Health and Human Service's Office of Minority Health, the National Institutes of Health and others in preparations for the meeting. We expect that participants will include those with expertise in minority health, clinical trials research, public health policy and other relevant disciplines.

2.2 Implementing efforts to enhance appropriate use of enrollment criteria in clinical trial protocols (*Short-term completion goal*)

Enrollment criteria define the study population for whom the researchers hope the benefits of a medical product will outweigh its risks while reasonably reflecting those populations who are likely to use the product once it is available on the market. Study enrollment criteria may unintentionally exclude certain demographic groups, thereby limiting useful information about product performance in diverse populations. We regularly encourage sponsors to incorporate meaningful inclusion of demographic subgroups in clinical studies so that the study participants reasonably reflect the populations who will be using the products if they are approved. The public may not be aware that these interactions take place between FDA and industry because such premarket meetings are confidential.

Action Item:

- ✓ We plan to work with industry to help ensure appropriate use of exclusion criteria in clinical trial protocols.

To better ensure that medical products are studied in the range of patients who will ultimately use them, FDA medical product centers are launching efforts to work more closely with industry to help ensure appropriate use of enrollment criteria in clinical trial protocols. As noted, older

patients (those over the age of 65) may have been excluded from clinical studies in diseases or conditions that affect them. An age limit of 65 years can lead to disproportionate exclusion of women in cardiovascular trials, yet women typically develop heart disease at an older age than men. CDER recently issued a Good Review Practice manual of policies and procedures (MAPP) that draws attention to such exclusion and other types of unnecessary exclusions. Such exclusions can also affect patients with disabilities or with multiple comorbid conditions. This initiative will further educate FDA reviewers and industry about methods to address the identification of and removal of unnecessary exclusions, with the goal of leading to trials that assess safety and effectiveness in a more representative segment of the intended use population.

2.3 Collaborating with NIH, industry, and other interested stakeholders to broaden diverse participation in clinical research (*Short-term and intermediate-term completion goal*)

We are encouraged by recent efforts on the part of industry to improve clinical trial participation—especially as it relates to minority and elderly patients—through partnerships with advocacy groups, consortia and a greater focus on community-based participatory research. FDA aims to support these broader efforts through a formal collaboration with NIH and other federal partners, as well as working with advocacy groups, medical associations, industry, and other stakeholders to increase the awareness of patients, specifically women, racial and ethnic minorities and the elderly, about the value of participating in clinical research and its role in moving safe and effective products to market.

Action Items:

- ✓ We plan to establish a joint working group with the National Institutes of Health Inclusion Policy Officer to establish a framework of collaboration and information exchange on inclusion policies, practices and challenges. This new working group will explore educational tools and outreach mechanisms to more broadly engage subgroups that consistently have low participation rates in clinical trials.
- ✓ OWH plans to collaborate with the NIH Office of Research on Women’s Health (ORWH) on a national campaign to educate and promote the importance of clinical trial participation, focusing on women. The two government organizations intend to develop partnerships with national organizations for outreach to their membership.
- ✓ We plan to work with industry to develop and share best practices related to recruiting a broad representation of patients for clinical research supporting FDA medical product applications.

We heard from a variety of companies developing medical products, as well as clinical research organizations, about successful strategies for recruiting a range of patients for biomedical research. Ideas to be explored include the development of plans in the early stages of medical product development to address the intended population and to share with FDA in early interaction meetings.

2.4 Using FDA’s communication channels to encourage clinical trial participation by demographic subgroups (*Short-term completion goal*)

FDA communicates to the public, including demographic subgroups, through a variety of channels including email, Twitter, Facebook, FDA Consumer Updates (which are similar in content to news articles) and the FDA Voice Blog, and by distributing various educational materials to our stakeholders. In addition, both OMH and OWH provide targeted outreach to stakeholders and make available a wealth of content on their own Web pages and on the dedicated Web page for Section 907.

Action Items:

- ✓ We plan to explore various ways to communicate to demographic subgroups about clinical trial participation. We envision that steps will include updating information about clinical trial participation on FDA’s website and distributing a new patient brochure.
- ✓ We plan to issue an FDA Consumer Update on clinical trial participation by demographic subgroups and distribute it to FDA’s subscriber list (approximately 140,000 subscribers) and to our targeted media list in both English and Spanish versions.

Priority Three: Making demographic subgroup data more available and transparent (Transparency)

We will aim to make demographic data more available and transparent by:

- 3.1 Posting demographic composition and analysis by subgroup in pivotal clinical studies for FDA-approved medical products;**
- 3.2 Identifying potential methods to consistently communicate meaningful information on demographic subgroups in medical product labeling;**
- 3.3 Implementing communication strategies that are sensitive to the needs of underrepresented subpopulations, with a focus on language access and health literacy; and**
- 3.4 Establishing an internal FDA steering committee to oversee and track implementation of the action plan and serve as planning group for an FDA workshop on the action plan.**

Stakeholders repeatedly told us that information about demographic subgroups is not easily accessible, nor is it in a format that could be readily understood by patients or health professionals when making treatment decisions.

We agree that FDA needs to do more to improve public understanding about how the agency assesses information about such data and how it relates to public health. Because much of this information already exists, but is buried within medical product reviews on FDA’s Web site, we will be taking significant steps to extract the data and make it readily available to the public. We are also considering how to consistently communicate meaningful information on demographic subgroups in medical product labeling, as applicable.

FDA is forming an internal working group to oversee this effort and all of the action items in this plan. In an effort to be transparent, the working group will regularly report its progress to the public. We also plan to convene a workshop within 18 months after the release of this action plan to review progress and obtain stakeholder input.

3.1 Posting demographic composition and analysis by subgroup in pivotal clinical studies for FDA-approved medical products (*Short-term and intermediate-term completion goal*)

Researchers, health professionals, and patients want access to data describing demographic subgroups included in clinical research and subgroup analyses, and want to know whether these analyses have resulted in clinically relevant findings.

Although the demographic composition and subgroup analyses are already included in medical product reviews located on FDA's Web site, they can be difficult to locate. In response to public feedback and in an effort to be more transparent, FDA is considering how to make this information more accessible.

Action Items:

- ✓ CDER and CBER plan to post demographic information from pivotal clinical studies for newly-approved drugs and biologics, such as New Molecular Entities and Biologics License Applications. We expect that this information will be excerpted from the medical product reviews or provided through hyperlinks to specific information in the medical product reviews and made available on a special Web page.
- ✓ FDA plans to explore approaches for public user-friendly ways of posting demographic information from medical device pivotal studies and completed post-approval and postmarket surveillance studies.

3.2 Identifying potential methods to consistently communicate information on demographic subgroups in medical product labeling (*Intermediate-term completion goal*)

Although we believe publishing demographic data collection and analyses on our Web site is an expeditious, simple and cost-effective way to share information, we acknowledge that stakeholders are also interested in how the labeling for medical products reflects this information. Current practice for labeling focuses on communicating as concisely as possible the information needed to safely and effectively use a medical product while minimizing extraneous information that may not be meaningful to guide clinical care or patient decision-making. The public has provided feedback that patients and health care providers also want information about the clinical trial population and the analysis of subgroups (e.g., if demographic analyses were performed; whether there were differences found among subgroups; and whether subgroup analyses were inconclusive due to limitations of sample size or missing data).

Action Items:

- ✓ We intend to work with industry, advocacy groups, risk communicators (including FDA's Risk Communication Advisory Committee) and other stakeholders to explore potential methods for communicating meaningful information on demographic analyses to the public.

For example, a standard set of concise statements could be developed for labeling.

As discussed at the public hearing, it will also be important to assess unintended consequences¹² that could result, for example, when data are inconclusive regarding a demographic subgroup.

- ✓ CDRH plans to conduct a study with health care professionals to improve usability and understanding of medical device labeling and product instructions for use.

Drawing on the test results, we envision that future guidance documents will contain a section that includes a discussion of the importance of meaningful information on demographics.

We envision that this section of guidance would address not only what is considered the standard demographics of age, gender, ethnicity and race, but also demographics that should be addressed in the design and testing of a device that are important to safe device use (e.g., cultural backgrounds of the intended patients and how they understand graphics, pictures and symbols; health literacy including languages; morbidities and co-morbidities of the user; physical capabilities and disabilities of the user; and cognitive abilities).

3.3 Implementing communication strategies that are sensitive to the language and health literacy needs of underrepresented subpopulations (*Short-term and intermediate-term completion goal*)

FDA recognizes that many subpopulations may have limited English proficiency and thus be unaware of certain health warnings. FDA has been working hard to make more of its written materials available to non-English-speaking consumers or to those for whom English is a second language. For example, press releases, FDA Consumer Updates, and drug safety communications considered of interest to the Latino community are routinely translated into Spanish. FDA translates materials into other languages on a case-by-case base, depending on the issue, although these are often limited due to resource constraints.

FDA is interested in identifying more effective ways to communicate so that patients and consumers, including those with low health literacy and limited English proficiency are better able to use medical products safely and effectively.

Action Item:

- ✓ We plan to implement communication strategies that are sensitive to the needs of underrepresented subpopulations, with a focus on language access and health literacy. FDA first addressed this subject in a report in response to Section 1138 of FDASIA.

¹² An example of an unintended consequence might be that a patient decides to stop taking a critical medical product based on incomplete information. Patients should always consult their health care professionals before stopping a medication.

3.4 Establishing an internal FDA steering committee to oversee and track implementation of the action plan (*Short-term completion goal*)

To be successful, we need leadership going forward to implement this action plan. Thus, we are establishing a new internal steering committee led by the Office of the Commissioner that will be given the responsibility for overseeing the plan's implementation.

Action Items:

- ✓ We plan to establish an agency-wide steering committee to oversee implementation of the action plan. The committee is expected to consider details for implementing the 27 action items as well as possible metrics for measuring progress, information that will be reported on a regular basis on the Section 907 Web page.
- ✓ We envision that the steering committee will also begin planning for a public workshop to be held within 18 months of the publication of the action plan where both FDA and the public can discuss what progress has been made in implementing the plan.

CONCLUSION

The *FDA Action Plan to Enhance the Collection and Understanding of Demographic Subgroup Data* reflects our continuing commitment to encouraging the inclusion of a diverse subject population in biomedical research used to support marketing applications for FDA-regulated medical products. It is clear that when diverse populations of subjects are involved in clinical research, we all benefit from a more complete knowledge base about the safety and effectiveness of medical products.

FDA agrees that greater representation of diverse populations in applications for FDA-regulated medical products is beneficial. By improving data quality, encouraging greater participation in clinical trials, and making demographic subgroup data more available and transparent, we can help to ensure that researchers, health professionals and consumers will have easy access to meaningful clinical information about medical products that will help them make informed decisions. FDA also acknowledges that the inclusion of diverse populations, obtaining better data, and communicating information to the public is a multifaceted problem that requires a multifaceted approach and the active participation of multiple stakeholders. FDA is committed to working with our many interested stakeholders on these important issues. This action plan is the first step in this process.

APPENDIX A: FDA Action Plan at a Glance

The action plan reflects FDA’s commitment to encourage the inclusion of a diverse patient population with regard to sex, age, race and ethnicity in biomedical research used in marketing applications for FDA-regulated medical products.

	Priority One: Quality—improving the completeness and quality of demographic subgroup data	Actions	Time frame
1.1	<i>Reviewing and developing a work-plan for updating, and/or finalizing, relevant guidance on demographic subgroup data, including FDA staff training and outreach to external stakeholders, as needed, for implementation</i>	<p>-CBER and CDER plan to review, update, and/or finalize, as needed, relevant industry guidance and internal FDA good review practice documents to encourage greater demographic subgroup representation in clinical trials, subgroup analysis and communication of results.</p> <p>-FDA plans to incorporate recommendations from the Evaluation of Sex-Specific Data guidance into reviewer templates, to provide staff training and develop and offer an external webinar on use of the guidance.</p> <p>-FDA plans to begin drafting a guidance document on analysis and reporting of ethnicity, race, and age in medical device clinical studies.</p>	<i>Short-term and intermediate-term completion goal</i>
1.2	<i>Working with sponsors to revise medical product applications to enhance information on demographic subgroups in medical product applications</i>	-CDER and CBER plan to revise the guidance on the Integrated Summary of Effectiveness sections of NDAs and BLAs.	<i>Intermediate-term completion goal</i>
1.3	<i>Strengthening FDA reviewer training by adding education/training around demographic inclusion, analysis and communication of clinical data</i>	<p>-FDA plans to require training for new clinical trial reviewers on the importance of demographic subgroup data inclusion, analysis, and communication.</p> <p>-FDA plans to offer additional education and training courses for experienced reviewers and other staff to better clarify FDA’s data collection and analysis expectations related to demographic subgroups.</p>	<i>Intermediate-term completion goal</i>
1.4	<i>Enhancing FDA’s systems for collecting, analyzing and communicating diverse clinical information to optimize safe and</i>	-FDA plans to work, to the extent possible, towards better standardization of data collection categories for age, racial and	<i>Intermediate-term to long-</i>

	<i>effective use of medical products in diverse populations over the total product life cycle</i>	<p>ethnic groups in submitted applications to facilitate harmonized data collection and analysis of subgroup outcome trends.</p> <p>-FDA plans to revise MedWatch forms to enable a standardized collection of demographic information on possible adverse events that occur after medical products are broadly available on the U.S. market.</p> <p>-FDA plans to strengthen systems and infrastructure for making better use of data once products are broadly available on the U.S. market.</p>	<i>term completion goal</i>
1.5	Conducting research on specific areas of public health concern related to demographic subgroups	<p>-Office of Women’s Health (OWH) plans to develop a new women’s health research roadmap that will help to better coordinate research across the agency and target OWH funding to projects that answer specific regulatory research questions and emerging priorities from the product review centers.</p> <p>-Office of Minority Health (OMH) plans to develop research projects leading to better understanding of medical product clinical outcomes in racial/ethnic demographic subgroups.</p> <p>-OMH plans to collaborate with NIH’s National Human Genome Research Institute in research into the role of genetics and genomics in health disparities.</p> <p>-As resources allow, FDA plans to develop a program of directed research in which FDA investigators could select a certain disease category and conduct an in-depth look at the data contained in relevant applications submitted over a specified time period (i.e., 5 to 10 years).</p>	<i>Intermediate-term completion goal</i>
	Priority Two: Participation—identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation	Actions	Time frame
2.1	Seeking further clarity about barriers to subgroup participation rates	-OMH plans to convene a meeting of experts in 2015 to better understand contemporary barriers to participation of minorities in clinical trials.	<i>Short-term completion goal</i>

2.2	Implementing efforts to enhance appropriate use of enrollment criteria in clinical trial protocols	-FDA plans to work with industry to try to ensure appropriate use of enrollment criteria in clinical trial protocols.	<i>Short-term completion goal</i>
2.3	Collaborating with NIH, industry and other interested stakeholders to broaden diverse participation in clinical research	<p>-FDA plans to establish a joint working group with the National Institutes of Health Inclusion Policy Officer to establish a framework of collaboration and information exchange on inclusion policies, practices and challenges.</p> <p>-OWH plans to collaborate with NIH Office of Research on Women’s Health on a national campaign to educate and promote the importance of clinical trial participation, focusing on women.</p> <p>-FDA plans to work with industry to develop and share best practices related to recruiting a broad representation of patients for clinical research supporting FDA medical product applications.</p>	<i>Short-term and Intermediate-term completion goal</i>
2.4	Using FDA’s communication channels to encourage clinical trial participation by demographic subgroups	<p>-FDA plans to explore various ways to communicate to demographic subgroups about clinical trial participation.</p> <p>-FDA plans to issue an FDA Consumer Update on clinical trial participation by demographic subgroups and distribute it in both English and Spanish versions to FDA’s subscriber list (approximately 140,000 subscribers) and to our targeted media list.</p>	<i>Short-term completion goal</i>
Priority Three: Transparency—making demographic subgroup data more available and transparent		Actions	Time frame
3.1	Posting demographic composition and analysis by subgroup in pivotal clinical studies for FDA-approved medical products	<p>-CDER and CBER plan to post demographic information from pivotal clinical studies for newly-approved medical products such as New Molecular Entities and Biologics License Applications.</p> <p>-FDA plans to explore approaches for public user-friendly ways of posting demographic information from medical device pivotal studies and completed post-approval and postmarket surveillance studies.</p>	<i>Short-term and Intermediate-term completion goal</i>

3.2	<i>Identifying potential methods to consistently communicate information on demographic subgroups in medical product labeling</i>	<p>-FDA intends to work with industry, advocacy groups, risk communicators (including FDA’s Risk Communication Advisory Committee), and other stakeholders to explore potential methods for communicating meaningful information on demographic analyses to the public.</p> <p>-CDRH plans to conduct a study with health care professionals to improve usability and understanding of medical device labeling and product instructions for use.</p>	<i>Intermediate-term completion goal</i>
3.3	<i>Implementing communication strategies that are sensitive to the language and health literacy needs of underrepresented populations</i>	-FDA plans to implement communication strategies that are sensitive to the needs of underrepresented subpopulations, with a focus on language access and health literacy.	<i>Short-term and Intermediate-term completion goal</i>
3.4	<i>Establishing an internal FDA steering committee to oversee and track implementation of the action plan</i>	<p>-FDA plans to establish an agency-wide steering committee to oversee implementation of the action plan.</p> <p>-FDA envisions that the Steering Committee will begin planning for a public workshop to be held within 18 months of the publication of the action plan.</p>	<i>Short-term completion goal</i>

APPENDIX B: Building the Necessary Knowledge Base

Understanding the Assessment of Patient or Population Characteristics in Medical Product Applications

An integral component of medical product development and application review is the assessment of patient or population characteristics that are relevant to the safety or effectiveness of a product. FDA reviewers—physicians, pharmacists, biomedical engineers, statisticians and other scientists—are constantly engaged with sponsors throughout the lifecycle of a product to evaluate these characteristics. From initial animal studies, to studies looking at pharmacokinetic (PK) data and the intervention in healthy populations, to studies in populations with the disease, and finally, in the postmarket setting, FDA looks at safety and effectiveness data for the overall population included in clinical trials and from other sources, and also by demographic subgroup. Based on these assessments, FDA may decide that further study is needed.

Because there are different regulatory authorities and approaches for drugs, biologics and devices, the collection; review and analysis; and communication of demographic subgroup information differs from FDA center to center. Outlined below is a brief description of how drugs, biologics and medical devices are assessed for patient or population characteristics.

A. Drugs/Biologics

Peoples' responses to pharmaceuticals are extremely variable. Common factors causing different responses may include body mass, kidney or liver function or how the body absorbs or metabolizes a drug. However, often the source of variability is not understood. (For example, why only a few patients in some cases experience a certain side effect.) During drug development, many studies are carried out with the goal of sorting out what factors may be leading to a lower treatment response or increasing the risk of a specific side effect.

Broadly speaking, differences in response to a treatment among individuals can be based on differences in pharmacokinetics (differences in blood levels of the drug) or pharmacodynamics (differences in how a patient responds to the same blood level) of a drug. PK differences are easily identified in drug studies because it is generally easy to measure blood levels and to examine the effect on blood levels of such factors as:

- Body size
- Kidney function
- Liver function
- Enzymes in the body that metabolize the drug, which can differ from patient to patient
- The effect of other drugs a patient may be taking that could be altering the absorption metabolism, or excretion of the study drug
- Age or gender

It is now standard practice in drug development to test, in targeted studies, how a drug is removed from the body (excreted in urine) or metabolized to an inactive substance (excreted in bile). It is also standard practice to identify other drugs that could interfere with these processes. This understanding makes it possible for a doctor to adjust the dose of a drug to a specific individual, thus reducing or eliminating the effects of PK characteristics

or drug-drug interactions. It is also usual today to measure blood levels in patients (population pharmacokinetics), enabling discovery of other, unexpected effects on the pharmacokinetics of a drug.

What is generally more difficult to discover and characterize are differences in pharmacodynamic (PD) response among patients; that is, why different patients respond differently to the same drug. In some cases, these *clinical differences* can be anticipated based on mechanistic considerations. For example, a patient whose elevated blood pressure is caused by high renin levels will respond better to certain antihypertensives than will a patient with low renin hypertension—and renin status can be related to race. However, in many cases, the reasons for response differences are not known. One way to detect such differences is to determine whether they are associated with certain recognized patient characteristics, including the demographic characteristics of age, sex and race, as well as other factors, such as concomitant illness, or disease severity.

FDA regulations¹³ require sponsors to include in their marketing applications analyses of effectiveness and safety by age, gender, and race and any other pertinent characteristics. As FDA documented in its Section 907 Report, sponsors almost always carry out these analyses, and FDA reviewers are closely attentive to such analyses. In some cases, critical differences from subgroup to subgroup have been detected. Some examples are:

1. Females are more likely to experience *torsades de pointes* than men.
2. The antihypertensive drug amlodipine caused increases in several dose-related adverse effects, and women had markedly higher rates of these adverse effects, as described in amlodipine’s labeling. (This finding led to a difference in recommended dosages for men and women.)

Adverse Event	Amlodipine		Placebo	
	Male (%) N = 1218	Female (%) N = 512	Male (%) N = 914	Female (%) N = 336
Edema	5.6	14.6	1.4	5.1
Flushing	1.8	4.8	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

3. In two early, well-controlled trials in the Veterans Health Administration system, BiDil, a combination of isosorbide dinitrate and hydralazine, appeared very effective in self-identified Blacks for the treatment of heart failure, but had a far smaller effect in Whites. The definitive study of BiDil, A-HEFT was carried out in the Black population and showed an over 40% reduction in mortality when BiDil was added to standard therapy. The drug product was labeled for use in self-identified Blacks.
4. Guidances developed by FDA and by ICH on studies in the elderly identify the elderly as potentially more sensitive to sedative-hypnotics. Developers for hypnotic drugs carry out separate studies in the elderly,

¹³ See 21 CFR 314.50.

and both PK and PD differences have been identified, generally leading to lower recommended doses in elderly patients.

When safety and/or effectiveness differences emerge from one subgroup of patients to another, it is critical to explain them. In some cases, a genetic difference has been shown to affect a person's metabolism, leading to an increase of a drug in blood levels or a failure to form an active metabolite. When additional testing and analysis can explain such differences, this information is added to the *knowledge base* for that therapy, and it may even become possible to individualize or personalize treatment using the therapy. Increasingly, drugs are being developed to treat a specific subgroup of patients, for example, patients with tumors having specific genetic characteristics or patients with particular genetic variants of other diseases, such as cystic fibrosis or Hepatitis C.

B. Medical Devices

The legal framework for medical device regulation is a risk-based standard for a broad range of technologies, which underscores the importance of nonclinical as well as clinical data in assessing medical device performance, and which adheres to *least burdensome* principles.¹⁴

A medical device can range from something as simple as a tongue depressor to something as complex as robotic surgery systems and from single-use to permanently-implanted heart valves. Technological advancements have led to a proliferation of minimally invasive device alternatives to surgical procedures, implantable stimulator device alternatives to long-term drug therapy, devices that step in for failing organs, lost limbs, and more. With early clinical experience, manufacturers often find ways to modify and improve a device, to make it smaller, more flexible and more durable, to enable use in a broader range of patients. Thus, medical device evaluation presents unique regulatory challenges related to greater diversity of medical devices, rapid technological advances, and the iterative nature of product development.

For higher risk devices, manufacturers provide FDA with clinical trial data as a component of the valid scientific evidence required to demonstrate a reasonable assurance of safety and effectiveness for its conditions of use. Lower risk devices in many cases do not require clinical data. Many attributes of a medical device can play a major role in the performance, safety, or effectiveness of the device. These attributes are routinely assessed via engineering tests. For example, for some implants, highly informative evidence about long-term performance comes from engineering tests that are able to challenge the device under worst-case conditions, test the device to failure, and simulate many years of use.

Clinical study populations for medical devices often reflect conditions of use that are limited to certain subpopulations, in part due to device eligibility constraints (e.g., surgical, anatomical or size limitations). Some studies evaluate a medical procedure only in patients who do not respond to available drugs or other treatments. In such groups, reliable information on incidence or prevalence of disease may not exist.

¹⁴ Most original PMAs and some supplements require clinical data to meet the statutory threshold for approval. Where clinical outcome can be reliably predicted from non-clinical data, however, well-designed bench and/or animal testing can be the basis for approval of the PMA. The cases when non-clinical data can meet the threshold for approval typically involve devices or modifications of approved devices for which scientifically valid information is available in the public domain. If clinical data are needed, FDA and industry will consider alternatives to randomized, controlled clinical trials, especially when potential bias associated with alternative controls can be eliminated.

Because many aspects of device performance can be evaluated with non-clinical testing, FDA can only impose the least burdensome data requirements.¹⁵ Moreover, because of their nature, many medical device clinical studies enroll fewer patients than drug trials. Therefore, it is often difficult to ensure that all demographic groups are represented in premarket studies—in many cases, to have broad demographic representation would require larger clinical studies. If the size of device clinical trials were required to be larger, trials would last much longer and cost much more. This could lead to fewer important devices being marketed in the United States. A more pragmatic and effective approach would be to enhance FDA's systems for collecting, analyzing and communicating information across the product life cycle. This approach can optimize safe and effective use of medical devices in diverse populations.

C. Identifying Trends

When premarket or postmarket differences or trends emerge in different subgroups of patients and when these differences can be explained through additional scientific examination and analysis, they add to the foundation of knowledge that is leading to personalized medicine. When a signal in a clinical trial is first detected indicating that variability exists between two subgroups of patients, this signal leads to further assessments and questions. Questions could include: Is there a genetic reason why certain patients react differently to the treatment? Is there a biomarker that could help predict which patients are more likely to have a certain response?

D. Personalized Medicine

Advances in science are driving the development of innovative medical products that are being used to treat small subsets of patients. For example, important discoveries about the role of cell growth and oncogenes in cancer set the stage for the development and approval in 1998 of trastuzumab (Herceptin), the first genetically guided therapy for the treatment of HER2-positive metastatic breast cancers.¹⁶ Personalized medicine generally involves the use of two medical products—typically, a diagnostic device and a therapeutic product—that work together to improve patient outcomes. These products are helping overcome the challenges of the one-size-fits-all model of patient treatment. Increasingly, a diagnostic device can be used to target a therapy to just the right patient, or subgroup of patients, in such a way that the benefits greatly outweigh the risks of treatment.

In a 2013 report, *Paving the Way for Personalized Medicine, FDA's Role in a New Era of Medical Product Development*,¹⁷ FDA describes the ways in which FDA has worked to respond to, anticipate, and help drive scientific developments in personalized therapeutics and diagnostics. The report provides a compendium of FDA's many recent efforts to advance regulatory standards, methods, and tools in support of personalized medicine and to further refine critical regulatory processes and policies to bring about personalized medical product development. Making sure that different demographic subgroups are sufficiently represented in clinical trials and enhancing the analyses and public availability of subgroup data will contribute to development of a

¹⁵ <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm>

¹⁶ In just the last three years, FDA approved four cancer drugs for use in patients whose tumors have specific genetic characteristics that are identified by a companion diagnostic test. In 2012, FDA approved a new therapy for use in certain cystic fibrosis patients with a specific genetic mutation. In 2013, three-dimensional (3D) printing was used to create a bioresorbable tracheal splint for treating a critically-ill infant.

¹⁷ This report is available on FDA's Web site at <http://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf>, accessed July 3, 2014.

sound knowledge base as we move toward a time when all stages of patient care – from prevention to diagnosis to treatment to follow-up—are truly personalized.

APPENDIX C: Statutory Language, Section 907 of FDASIA

SEC. 907. REPORTING OF INCLUSION OF DEMOGRAPHIC SUBGROUPS IN CLINICAL TRIALS AND DATA ANALYSIS IN APPLICATIONS FOR DRUGS, BIOLOGICS, AND DEVICES.

(a) REPORT.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this Act, the Secretary, acting through the Commissioner, shall publish on the Internet web site of the Food and Drug Administration a report, consistent with the regulations of the Food and Drug Administration pertaining to the protection of sponsors' confidential commercial information as of the date of enactment of this Act, addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to the Food and Drug Administration, and shall provide such publication to Congress.

(2) CONTENTS OF REPORT.—The report described in paragraph (1) shall contain the following:

- (A) A description of existing tools to ensure that data to support demographic analyses are submitted in applications for drugs, biological products, and devices, and that these analyses are conducted by applicants consistent with applicable Food and Drug Administration requirements and Guidance for Industry. The report shall address how the Food and Drug Administration makes available information about differences in safety and effectiveness of medical products according to demographic subgroups, such as sex, age, racial, and ethnic subgroups, to health care providers, researchers, and patients.
- (B) An analysis of the extent to which demographic data subset analyses on sex, age, race and ethnicity is presented in applications for new drug applications for new molecular entities under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), in biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262), and in premarket approval applications under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e) for products approved or licensed by the Food and Drug Administration, consistent with applicable requirements and Guidance for Industry, and consistent with the regulations of the Food and Drug Administration pertaining to the protection of sponsors' confidential commercial information as of the date of enactment of this Act.
- (C) An analysis of the extent to which demographic subgroups, including sex, age, racial, and ethnic subgroups, are represented in clinical studies to support applications for approved or licensed new molecular entities, biological products, and devices.
- (D) An analysis of the extent to which a summary of product safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity is readily available to the public in a timely manner by means of the product labeling or the Food and Drug Administration's Internet web site.

(b) ACTION PLAN.—

(1) IN GENERAL.—Not later than 1 year after the publication of the report described in subsection (a), the Secretary, acting through the Commissioner, shall publish an action plan on the Internet web site of the Food and Drug Administration, and provide such publication to Congress.

(2) CONTENT OF ACTION PLAN.—The plan described in paragraph

(1) shall include—

- (A) recommendations, as appropriate, to improve the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling;
- (B) recommendations, as appropriate, on the inclusion of such data, or the lack of availability of such data in labeling;
- (C) recommendations, as appropriate, to otherwise improve the public availability of such data to patients, health care providers, and researchers; and
- (D) a determination with respect to each recommendation identified in subparagraphs (A) through (C) that distinguishes between product types referenced in subsection (a)(2)(B) insofar as the applicability of each such recommendation to each type of product.

APPENDIX D: Relevant FDA Regulations/Guidance to Industry on Collection, Analysis, and Availability of Subgroup Data¹⁸

TABLE 1. DESCRIPTION OF STATUES AND REGULATIONS BY CENTER			
YEAR	CENTER	FDA REGULATION	DIRECTION
1985	CDER	Content and Format of a New Drug Application. 21 CFR 314.50 [1]	Requires effectiveness data be presented by gender, age and racial subgroups and dosage modifications be identified for specific subgroups. Also requires safety data be presented by gender, age and racial subgroups; and that safety data from other subgroups of the populations of patients treated be presented, as appropriate.
1997	CDER/CBER	Food and Drug Administration Modernization Act (FDAMA) Sec. 115 Clinical Investigations (b) Women and Minorities—Sec. 505(b)(1;);) 21 U.S.C 355 (b) (1) [2]	Requires that FDA and the National Institutes of Health (NIH), along with representatives of the drug manufacturing industry, review and develop guidance on inclusion of women and minorities in clinical trials.
1998	CBER/CDER	Investigational New Drug Applications. 21 CFR 312.33 [3]	Requires that investigational new drug (IND) data regarding participation in clinical trials be presented in annual reports by sex, age, and race.
2002	Agency-Wide	Best Pharmaceuticals for Children Act [4]	Provides mechanisms for studying on- and off-patent drugs in children; seeks to improve the level of information in scientific publications and/or the label about pharmaceuticals used to treat children. Reauthorized in 2007, permanent reauthorization under FDASIA 2012.
2003	CBER/CDER	Pediatric Research Equity Act [5]	Requires that NDAs and biologics license applications (BLAs) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment, unless the applicant has obtained a waiver or deferral. Reauthorized in 2007, permanent reauthorization under FDASIA 2012.
2007	Agency-Wide	Food and Drug Administration Amendments Act, Pub. L. no 110-85 [6]	Expanded clinical trials database; provided FDA authorities and resources for premarket and postmarket drug safety, including the authority to require postmarket studies and clinical trials, safety labeling changes and Risk Evaluation and Mitigation Strategies (REMS).

¹⁸ As of July 1, 2014

TABLE 1. DESCRIPTION OF STATUES AND REGULATIONS BY CENTER			
YEAR	CENTER	FDA REGULATION	DIRECTION
2007	CDER/CDER	Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products. 21 CFR 201.56 [7]	Requires prescription drug products (including biological products that are regulated as drugs) to contain specific information about use in specific populations in the contents of drug labeling.
2012	CDRH	Labeling for In Vitro Diagnostics Products. 21 CFR 809.10 [8]	Recommends that sponsors include information about the demographics of study populations in labeling.
2013	CDRH	Medical Devices; Pediatric Uses of Devices; Requirement for Submission of Information on Pediatric Subpopulations That Suffer From a Disease or Condition That a Device Is Intended To Treat, Diagnose, or Cure. 21 CFR 814 [9]	Amends the regulations on premarket approval of medical devices to include requirements relating to the submission of information on pediatric subpopulations that suffer from the disease or condition that a device is intended to treat, diagnose or cure.
CFR: CODE OF FEDERAL REGULATIONS			

TABLE 2. FDA GUIDANCE DOCUMENTS BY CENTER			
YEAR	CENTER	GUIDANCE ¹⁹	DIRECTION
1988	CDER	Guideline for the Format and Content of the Clinical and Statistical Sections of an Application [10]	Recommends data analysis of safety, effectiveness and clinical pharmacology studies by sex, race and age.
1989	CDER	Guidance for industry: Study of Drugs Likely to be Used in the Elderly [11]	Recommends pharmacokinetic screen of Phase II/III trials and data analysis by age and sex.
1993	CDER	Guidance for industry: Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs [12]	Recommends pharmacokinetics and pharmacodynamics in women, pharmacokinetic screen as a tool to detect differences, analysis of safety and efficacy by sex.
1996	CDER/CDER	Guidance for industry: E6 Good Clinical Practice: Consolidated Guidance [13]	Provides a unified standard for the European Union (EU), Japan and the United States to facilitate mutual acceptance of clinical data by regulatory authorities. Guidance addresses pharmacokinetics, product metabolism, safety and effectiveness in population subgroups as appropriate (see Section 7.3.6).
1998	CDER/CDER	Guidance for industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products [14]	Provides guidance to applicants planning to file NDAs, BLAs, or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness. Guidance addresses studies of effectiveness in demographic subsets (see Section C (2)(c)).
1998	CDER/CDER	Guidance for industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products [15]	Intended to assist applicants planning to conduct pharmacokinetic studies in pediatric populations. The guidance addresses general considerations for conducting such studies so that drug and biological products can be labeled for pediatric use.
1999	CDER/CDER	Guidance for industry: Population Pharmacokinetics [16]	Recommends use of population pharmacokinetics to help identify differences in drug safety and effectiveness among population subgroups.
2000	CDER/CDER	Guidance for industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population [17]	Intended to encourage and facilitate timely pediatric medicinal product development internationally. The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.
2001	CDER/CDER	Guidance for industry: Content and Format for Geriatric Labeling [18]	Provides industry with information on submitting geriatric labeling of human prescription drug and biological products.

¹⁹ All guidance documents are available at: <http://www.fda.gov/regulatoryinformation/guidances/default.htm>

TABLE 2. FDA GUIDANCE DOCUMENTS BY CENTER			
YEAR	CENTER	GUIDANCE ¹⁹	DIRECTION
2005	Agency-Wide	Guidance for industry: Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products [19]	Recommends format for obtaining race and ethnicity information for U.S. and international clinical trials to be submitted for regulatory review to the FDA.
2005	CBER/CDER	Guidance for industry: How to Comply with the Pediatric Research Equity Act [20]	Provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act and addresses the pediatric assessment, the pediatric plan, waivers and deferrals, compliance issues, and pediatric exclusivity provisions.
2006	CBER/CDER	Guidance for industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products - Content and Format [21]	Assists applicants in deciding (1) what studies should be included in the CLINICAL STUDIES section of prescription drug labeling, (2) how to describe individual studies, and (3) how to present study data, including presentation of data in graphs and tables. Guidance is intended to make the CLINICAL STUDIES section of labeling, as described in the final rule amending the requirements for the content and format of labeling for human prescription drug and biological products (21 CFR 201.56 and 201.57), more useful and to promote consistency in the content and format of the section across drug product classes and within drug classes and indications.
2006	CBER	Guidance for industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications [22]	Provides recommendations on the conduct of developmental toxicity studies for investigational preventive and therapeutic vaccines for infectious disease indications. Guidance pertains to the assessment of the developmental toxicity potential of preventive and therapeutic vaccines for infectious diseases indicated for females of childbearing potential and pregnant individuals.
2008	Agency-Wide	Guidance for industry: Providing Regulatory Submissions in Electronic Format: Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications [23]	This is one in a series of guidance documents intended to assist applicants making regulatory submissions to FDA in electronic format using the electronic common technical document (eCTD) specifications. The eCTD guidance recommends application data, including demographic subgroup data information, be submitted in standardized electronic format.
2011	CDRH	Guidance for Industry and Food and Drug Administration Staff: Evaluation of Sex Differences in Medical Device Clinical Studies (draft) [24]	Provides guidance on the study and evaluation of sex differences in medical device clinical studies and outlines CDRH's expectations regarding sex-specific patient enrollment, data analysis and reporting of study information.

TABLE 2. FDA GUIDANCE DOCUMENTS BY CENTER

YEAR	CENTER	GUIDANCE ¹⁹	DIRECTION
2011	CBER/CDRH	Guidance for industry Clinical Investigators, and Food and Drug Administration Staff: Design Considerations for Pivotal Clinical Investigations for Medical Devices (draft) [25]	Provides guidance to those involved in designing clinical studies intended to support premarket submissions for medical devices. This guidance addresses subject selection and recommends sponsor discussion of potential issues with FDA in regards to clinical study involving vulnerable populations, such as pregnant women, in advance of study (See Section 6.4). Recommends stratified selection of subjects (e.g. by sex) for clinical study (see Section 6.5) and that study sites include subjects who reflect epidemiological distribution of the disease being treated with regard to variables such as sex (see Section 6.6) .

TABLE 3. FDA TOOLS FOR REVIEWERS

CENTER	TYPE OF TOOL	TOOL	DESCRIPTION
CBER	Standard Operating Policies and Procedures (SOPP)	SOPP 8412 Review of Product Labeling [26]	Outlines the general operating procedures for CBER staff in processing draft and final product labeling submissions.
CBER	Standard Operating Policies and Procedures (SOPP)	SOPP 8401.7 Action Package for Posting [27]	Serves as a guide for staff for the development and assembly of action packages for posting, pursuant to Section 916 of the Food and Drug Administration Amendments Act (FDAAA) of 2007.
CBER	Review Template	CBER Clinical Review Template (internal)	The clinical review template is intended to assist reviewers conducting the primary clinical review as part of the new biologics license application (BLA) or BLA supplement review process. The template is also meant to establish standardization and consistency in the format and content of primary clinical reviews and to ensure that critical presentations and analyses will not be inadvertently omitted. The standardized structure enables subsequent reviewers and other readers to readily locate specific information. Reviewers are instructed to discuss the results of analyses in special populations (e.g., pediatric patients, premature infants, the elderly and persons at exceptional risk for the health-related condition of interest).
CDRH	Review Checklist	Summary of Safety and Effectiveness (SSED) Clinical Section Checklist [28]	Intended to present a reasoned, objective and balanced summary of the scientific evidence, both positive and negative, that served as the basis of the decision to approve or deny the premarket approval application (PMA). This document discusses demographic subgroup data and analysis, including study population demographics and baseline parameters.
CDRH	Review Template	Premarket Approval (PMA) Application Statistical Review Assessment [29]	Used to standardize the structure of statistical review memos and ensure review quality in an in-depth review of a PMA for therapeutic devices or diagnostics. This document discusses demographic subgroup data and analysis, including whether important subgroups are identified and their planned analyses described.
CDRH	Review Template	Investigational Device Exemptions (IDE) Statistical Quality Review Assessment (Internal)	Used to standardize the structure of statistical review memos and ensure review quality in an in-depth review of an IDE for therapeutic devices or diagnostics. This document discusses demographic subgroup data and analysis, including whether baseline covariates that include demographic information and time-dependent covariates to be measured on subjects are clearly identified; and whether important subgroups are identified and their planned analyses described.
CDRH	Review Template	Medical Officer Review Template (Internal)	Used to standardize the structure of clinical review memos and ensure review quality in an in-depth review of an IDE for therapeutic devices or diagnostics. This document discusses demographic subgroup data and analysis, including whether important subgroups will be enrolled in the clinical study.

TABLE 3. FDA TOOLS FOR REVIEWERS

CENTER	TYPE OF TOOL	TOOL	DESCRIPTION
CDRH	Summary Form	Pivotal Investigational Device Exemption Descriptive Summary Form [30]	Completed by FDA reviewers as part of the IDE review process for pivotal trials to provide an accessible summary of the major trial design elements. This Summary helps CDRH achieve consistency in ensuring that an analysis plan is in place to evaluate sex differences in primary safety and effectiveness endpoints. It also aids CDRH in developing mechanisms to prospectively add and analyze current and future clinical trial metrics related to demographics.
CDRH	Review Template	Post-Approval Studies (PAS) (Internal)	Requires reviewers to evaluate if the sponsors have submitted study enrollment data by sex/gender, age groups and race/ethnicity. Depending on the study planned analysis, reviewers are also required to evaluate if subgroup analyses are submitted.
CDER	Quality Assessment Tool	CDER 21 st Century Review Process Desk Reference Guide [31]	Intended for use by both the applicant and members of CDER’s review team and designed to guide them through the pertinent sections of an application and to assist in assessing the content of the NDA/BLA submission as well as the overall review process
CDER	Review Checklist	Clinical Filing Checklist for NDA/BLA (Internal)	Used to determine if a submission is <i>fileable</i> (i.e., will be accepted for full review) and considers whether all data required by the regulations are included, specifically listing applicability of foreign data to the U.S. population.
CDER	Review Template	Clinical Review Good Review Practice Policy and Procedure (Manual of Policy and Procedures (MAPP) 6010.3) [32]	A structured outline and annotated table of contents used in the preparation of a clinical review, which outlines the organization of content, promotes consistency in the documentation of elements, and provides for ready retrieval of information. The template includes a sample table for demographic profile and the following review sections: <ul style="list-style-type: none"> ▪ Efficacy demographics ▪ Efficacy subpopulations ▪ Analysis of clinical information relevant to dosing ▪ Overall exposure at appropriate doses/duration & demographics of target populations ▪ Drug-demographic interactions ▪ Special safety studies ▪ Pediatrics

TABLE 3. FDA TOOLS FOR REVIEWERS

CENTER	TYPE OF TOOL	TOOL	DESCRIPTION
CDER	MAPP	Clinical Pharmacology and Biopharmaceutics Review Policy and Procedure (MAPP 4000.4) [33]	<p>States that the Clinical Pharmacology and Biopharmaceutics Review Template is to be used by all reviewers to document primary reviews of all original new drug application (NDAs) and supplemental NDAs (sNDAs) and establishes an outline for reviews of original NDAs and sNDAs. The template includes:</p> <ul style="list-style-type: none"> ▪ Elderly ▪ Pediatric patients ▪ Gender ▪ Race, in particular differences in exposure and/or response in Caucasians, African-Americans and/or Asians
CDER	Review Checklist	Statistics Filing Checklist for an Original NDA/BLA (Internal)	Ascertains whether safety and efficacy were investigated for gender, racial and geriatric subgroups prior to application acceptance <i>filing</i> for full review.

TABLE 3. FDA TOOLS FOR REVIEWERS

CENTER	TYPE OF TOOL	TOOL	DESCRIPTION
CDER	Review Template	Statistical Review and Evaluation Template (Internal)	<p>Describes the content of an NDA/BLA statistical review relevant to demographic data. In the <i>Findings in Special/Subgroup Populations</i> section the reviewer describes efficacy (safety) results across subgroups defined by gender, race, age, and geographic region. Other subgroups such as those based on baseline characteristics may be included, depending on their relevance, representation in the clinical studies or on the disease being reviewed. In the subsection entitled, <i>Gender, Race, Age, and Geographic Region</i>, the reviewer describes efficacy (safety) results across subgroups defined by gender, race, age (e.g., less than 65 versus greater than or equal to 65 years), and geographic region (e.g., U.S. vs. non-U.S.). The reviewer also includes descriptive statistics for the defined subgroups and inferential statistics such as the results of tests for treatment by subgroup interactions that may also be included. Significant interaction test results are fully explained, e.g., by including graphics depicting the results, and the reviewer exercises caution when synthesizing the data across studies.</p> <p>Scientifically valid methods are employed when drawing inferences from pooled data, and the impact of a subgroup difference may be briefly addressed here and more fully explained in a subsequent section, or vice versa. Mention is made if no conclusions can be drawn due to lack of representation, limited sample size, etc. If, for example, the studies were conducted in one gender only, a brief statement is indicated that gender analysis was not applicable. In the subsection entitled, <i>Other Special/Subgroup Populations</i>, other subgroups may be defined by baseline characteristics and are to be included depending on their relevance, on their representation in the clinical studies, or on the disease being reviewed. If no subgroups other than those in the previous sub-section are reviewed, the reviewer indicates here that no other subgroups were analyzed.</p>