

FDA Report

Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products August 2013



**U.S. Department of Health and Human Services
Food and Drug Administration**



Message from Dr. Margaret Hamburg Commissioner of Food and Drugs

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 included a requirement that FDA study the availability of data on the participation of demographic subgroups (sex, age, race, and ethnicity) in clinical trials that support applications for new drugs, biologics, and devices.

Specifically, Section 907 of FDASIA directed FDA to report on the extent to which subgroups participate in such trials, whether reports of subgroup safety and effectiveness are reported to FDA in a manner consistent with FDA requirements and guidance, and whether and how safety and effectiveness data by subgroup is eventually made public. We welcome the opportunity to take a closer look at the inclusion and analysis of demographic subgroups in applications for medical products.

An FDA-wide working group, tasked with the responsibility of producing the report, examined 72 product applications approved in 2011. I am pleased to announce that the report we are providing to Congress and posting on our Website today concludes that the statutes, regulations, and policies currently in place generally give product sponsors a solid framework for providing data in their applications on the inclusion and analysis of demographic subgroups. In general, sponsors are describing the demographic profiles of their clinical trial participants, and the majority of applications submitted to FDA include demographic subset analyses. We also found that FDA shares this information with the public in a variety of ways.

We look forward to hearing from patients, consumers, health care practitioners, industry, and others about this report. This input, as well as the report's key findings, especially its identified areas for improvement, will help inform our creation of an Action Plan, as required by Congress. Once we develop an Action Plan, we look forward to continuing to interact with all interested stakeholders as we implement the Action Plan.

Sincerely,

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

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Executive Summary

For many decades, U.S. governmental initiatives have sought to identify the best ways to advance the three ethical principles that underlie the conduct of biomedical research: respect for persons, beneficence and justice (which asks who ought to receive the benefits of research and bear its burdens).¹ Consistent with the principle of justice, FDA has a variety of statutory, regulatory, and policy-related tools that provide a framework for guiding medical product sponsors in the inclusion and analysis of demographic subgroups in clinical trials.

However, scientific advances in understanding the specific genetic variables underlying disease and response to treatment are increasingly becoming the focus of modern medical product development as we move toward the ultimate goal of tailoring treatments to the individual, or class of individuals, through personalized medicine. Thus, the broad, self-identified demographic subgroup categories used today may not adequately capture the complexity underlying responses to medical treatments. Nonetheless, it remains important that clinical trials include diverse populations, whenever possible and appropriate.

Last year Congress, in Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), directed FDA to produce a report that took a closer look at the inclusion and analysis of demographic subgroups. Specifically, Congress asked FDA to consider four key topic areas: tools to ensure submission of demographic information, subset analysis, demographic subgroup participation in clinical trials submitted to the FDA in support of product applications, and communication of this information to health care professionals and the American public.

To comply with that request, an FDA working group evaluated 72 applications approved during 2011 for new molecular entity² drug products, original biologics, and Class III devices (premarket approval). Their key findings, organized by topic area, are as follows:

Tools to ensure submission of demographic information

- Although there is some variation by product area, FDA's statutory and regulatory requirements, guidances, policies, and procedures generally inform sponsors about including tabulations of the demographic data on clinical trial participants and demographic subset analyses in their medical product applications (see Appendix 1).

¹ Ethical Principles and Guidelines for the Protection of Human Subjects of Research (The Belmont Report). Available at www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed July 30, 2013.

² A new molecular entity is an active ingredient that has never before been marketed in the United States in any form. Available at: <http://www.fda.gov/drugs/informationondrugs/ucm079436.htm> Accessed: May 15, 2013.

- Similarly, tools (e.g., application review templates and FDA standard operating policies and procedures) guide regulatory review staff in the assessment of marketing applications to ensure that demographic data and subset analyses are included in the information FDA uses in its review and approval processes.

Extent of demographic subset analyses

- The extent to which demographic subset data were analyzed varied across medical product types (drugs, biologics, and devices). Applications for drugs and biologics addressed subset analyses by sex, race, and age – that is, the applications mentioned demographic subsets in some way. The majority of the device applications contained a subset analysis for age and sex, with a lower percentage of applications containing a subset analysis for race or ethnicity. Inclusion did not necessarily mean that the data on patient subgroups was sufficient for meaningful analysis or to detect relevant subgroup effects. In some of the applications reviewed for this report, the results of the subgroup analyses were limited by low sample size.

Extent of demographic subgroup representation in clinical trials

- All biologics, drugs, and the majority of the medical device applications reviewed for this report 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 area. Although it is important to include diverse populations in clinical trials when possible and appropriate, the unique nature of medical devices means that this additional information would not always contribute to FDA's decision making. For example, certain microbiology in-vitro diagnostic devices (IVDDs) have high overall accuracy; when this occurs, additional analyses by subpopulations would not affect clearance or approval or clinical use.
- Whites represented a high percentage of clinical trial study participants for biologic, drug, and medical device applications. In many cases, other racial subgroups were underrepresented.

Communication of demographic subgroup information to the public

- FDA's internal policies and procedures and regulations facilitate the assessment of demographic subgroup information included in marketing applications. Moreover, following medical product approval, FDA can communicate available information to the public on the demographic profile of the study participants and on the demographic data subset analyses using a variety of mechanisms: initially with product labeling and publicly posted clinical reviews and later, once a product is on the market, with consumer updates, safety alerts, label changes, and other mechanisms, should this be necessary.

- Statutory differences in the regulatory framework for medical devices compared to those applicable to drugs and biologics account for differences in policies and practices across FDA centers with regard to submission and analysis of demographic data and public disclosure of information at the time a product is approved (e.g., timing of information, information release, and public documents).

The information gathered for this report will become a starting point for developing an Action Plan, to be released next year, as required under Section 907.

FDA Report

Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products

August 2013

Introduction

For many decades, U.S. governmental initiatives have sought to identify the best ways to advance the three ethical principles that underlie the conduct of biomedical research: respect for persons, beneficence, and justice (which asks who ought to receive the benefits of research and bear its burdens).³ Consistent with the principle of justice, FDA has a variety of statutory, regulatory, and policy-related tools that provide a framework for guiding medical product sponsors on the inclusion and analysis of demographic subgroups in clinical trials. This report describes these tools.

However, scientific advances in understanding the specific genetic variables underlying disease and response to treatment are increasingly becoming the focus of modern medical product development as we move toward the ultimate goal of tailoring treatment to the individual or class of individuals. Thus, the broad, self-identified demographic subgroup categories used today may not adequately capture the complexity underlying responses to medical treatments. Nonetheless, it remains important that clinical trials include diverse populations, whenever possible and appropriate.

On July 9, 2012, the President signed the Food and Drug Administration Safety and Innovation Act (FDASIA).⁴ Section 907 of FDASIA, Reporting of Inclusion of Demographic Subgroups in Clinical Trial and Data Analysis in Applications for Drugs, Biological Products, and Devices called for a report with the following requirements:

(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 (FDA) a report, consistent with the regulations of the FDA 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

³ Ethical Principles and Guidelines for the Protection of Human Subjects of Research (The Belmont Report). Available at www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed July 30, 2013.

⁴ Food and Drug Administration Safety and Innovation Act. Public Law No 112-144 (July 9, 2012). Available at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>. Accessed January 16, 2013.

effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to the FDA, and shall provide such publication to Congress.

(2) 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) Contents of the report – The report described in paragraph (1) shall contain the following:

- 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.*
- 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.*
- 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.*
- 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.*

This report addresses demographic subgroup participation in clinical trials submitted to FDA in support of product applications; it describes demographic data collection, subset analysis, and public communication of this information. FDA's next step will be to use the information gathered for this report as a starting point for developing an Action Plan also called for by Congress in Section 907. We look forward to input from patients, consumers, health care professionals, industry, and other stakeholders as we work to develop and implement the Action Plan.

Background

To prepare this report, FDA convened an FDA-wide working group led by the Office of Women's Health (OWH) in collaboration with the Office of Minority Health (OMH) and representatives from the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), the Office of Health and Constituent Affairs (OHCA), the Office of Pediatric Therapeutics (OPT), and other FDA offices. The working group undertook a systematic evaluation to complete the four tasks set out in the FDASIA legislation.⁵ As described in Section 907 requirements, the assessment was to include information derived from sponsor applications, FDA reviews, and product labeling.

The working group evaluated 72 applications approved during 2011 for new molecular entity⁶ drug products, original biological products, and Class III devices (premarket approval). These are collectively referred to in this report as *medical product applications* unless otherwise specified. The applications evaluated for this report included 24 drugs, 11 biologics (5 approved by CBER and 6 approved by CDER – for 7 indications),⁷ and 37 medical devices. Lists of the medical product indications approved in 2011 by CDER and CDRH and reviewed for this report are provided in Appendices 2 and 4, respectively; the indications for the five applications approved in CBER are listed in Part 1.

The number of applications reviewed by the working group for this report generally reflects the average number of approvals per year. To provide some context, from fiscal year (FY) 2000 to FY 2010, CBER approved 64 biologics license applications, ranging from 2 to 10 per year.⁸ For the 10-year period from calendar year 2002 through 2011, CDER averaged 24 novel new medicines, known as new molecular entities, approvals per year.⁹ In 2011, CDER approved 30 NMEs (for 31 indications) representing the second highest total in the past 10 years (except 2004, during which CDER approved 36 new molecular entities). These new molecular entities approved by CDER included applications for both new drug applications (NDAs) and biologics license applications (BLA). For the 10-year period from calendar year 2002 through 2011, CDRH averaged 30 premarket approvals (PMA) per year. CDRH approved 37 PMAs in 2011,

⁵ Ibid.

⁶ A new molecular entity is an active ingredient that has never before been marketed in the United States in any form. Available at: <http://www.fda.gov/drugs/informationondrugs/ucm079436.htm> Accessed: May 15, 2013.

⁷ One product was approved for two different indications .

⁸ See Biological Approvals by Year: Available at: <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/default.htm>. Accessed: February 19, 2013.

⁹ See 2011 Novel New Drugs. Available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM293663.pdf>. Accessed February 19, 2013.

representing the third highest total in the past 10 years (except 2004 and 2006, during which 47 and 39 PMAs were approved, respectively).¹⁰

The findings in this report may not be generalizable to all FDA-approved medical products. However, selection bias was minimized by including *all* medical product applications approved during 2011, regardless of indication, trial size, and other factors (e.g., orphan designation) that could influence the findings. Nevertheless, because of the nature of medical product development, the 2011 approvals actually represent a culmination of various development activities that may span many years. Thus, the data analyzed for this report represent clinical trial data accrued over time. Practical factors also informed our decision to look at a one-year sample.

The one-year statutory timeline to collect, analyze, write, clear, and publish this report was a challenge. For example, the working group had to manually abstract data from applications and other FDA documents to analyze the findings and compile the report within the allotted time frame. One approval decision for an application may have multiple sources of data that FDA staff needed to review to address the legislative requirements outlined in the section 907 of FDASIA.

Report Organization

Because the regulatory framework for drugs and biologics differs in important ways from that used for medical devices, the report is divided into two parts: **Part 1** of the report discusses drugs regulated by CDER¹¹ and biologics regulated by CBER¹² and CDER. These centers regulate drugs and biologics according to the Federal Food, Drug, and Cosmetic Act (FD&C Act)¹³ and the Public Health Service (PHS) Act,¹⁴ respectively. **Part 2** discusses medical devices,¹⁵ which are regulated primarily by CDRH.

¹⁰ PMA Approvals. Available at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/default.htm>. Accessed 5/9/2013.

¹¹ CDER regulates most therapeutic biologics products (e.g., recombinant products, such as enzymes and monoclonal antibodies) and drug products.

¹² CBER regulates a variety of medical products including allergenics, blood and blood components and blood derivatives, certain medical devices, gene therapy, human tissues, cellular products, vaccines, and xenotransplantation products.

¹³ The FD&C Act defines *drugs*, in part, by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and as "articles (other than food) intended to affect the structure or any function of the body of man or other animals" (FD&C Act, sec. 201(g)(1)). Available at <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapII-sec321.pdf>. Accessed April 4, 2013.

¹⁴ The Public Health Service Act (PHS Act) 1944. Available at <http://www.fda.gov/regulatoryinformation/legislation/ucm148717.htm>. Accessed March 7, 2013.

¹⁵ Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices. Additionally, medical devices include in vitro diagnostic products, such as general purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology. Certain electronic radiation-emitting products with medical application and claims meet the definition of medical device. Examples are diagnostic ultrasound products, x-ray machines, and medical lasers.

Following a brief overview of the tools FDA uses to facilitate the collection and analysis of demographic subgroup data, this report discusses the findings of the working group.

Tools to Ensure Analysis of Demographic Information

FDA uses a variety of tools to ensure the collection, submission, and analysis of demographic data with clinical trial data. Although there is no statutory or regulatory requirement to include demographic subgroups as participants in clinical trials, FDA guidance documents encourage,^{16, 17, 18} and regulations clearly require, presentation and inclusion of analyses of demographic data in marketing applications (see Appendix 1, Table 1). In 1985, FDA issued regulations on the content and format of new drug applications (21 CFR 314.50¹⁹) that require the presentation of effectiveness data by gender,²⁰ age, and racial subgroups and the identification of dosage modifications for specific subgroups. Those same regulations require safety data to be presented by gender, age, and racial subgroups, and when appropriate, safety data from other subgroups of the population of patients treated must also be presented. In 1998, FDA amended its investigational new drug application regulations (21 CFR 312.33²¹) to require that data on the participation in clinical trials be presented in annual reports by age group, gender, and race (see additional regulations in Appendix 1, Table 1).

FDA guidance documents provide additional policy recommendations relevant to the collection and analysis of relevant subgroup data in clinical trials (see the list in Appendix 1, Table 2). For example, in 1993, FDA issued guidance to encourage inclusion of women of childbearing potential in phase 1 and early phase 2 trials; made recommendations for the assessment of potential pharmacokinetic (PK) differences between genders; and encouraged sponsors to collect sex-related data during research and development and analyze the data for sex effects.²² In 2011, FDA issued draft guidance on evaluating sex differences in medical device studies, outlining

¹⁶ FDA guidance *E7 Studies in Support of Special Populations: Geriatrics, Questions and Answers*.

Note: FDA guidance documents are available at
<http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>

¹⁷ FDA guidance *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*

¹⁸ There is evidence that guidance has been successful in getting good sex demographic subgroup representation, as noted in Appendix 1 of FDA's *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*. One example is a follow-up GAO study from 2000, in which GAO noted that women are now included in clinical research at rates proportional to their representation in the population. (United States General Accounting Office, Report to Congressional Requesters. Women's Health, NIH Has Increased Its Efforts to Include Women in Research). Available at <http://www.gao.gov/archive/2000/he00096.pdf>. Accessed April 12, 2013.

¹⁹ Content and format of an application, 21 CFR Sect. 314.50 (2012). Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.50>. Accessed May 9, 2013

²⁰ The terms *sex* and *gender* have been used interchangeably in some FDA documents.

²¹ Annual reports, 21 Code of Federal Regulations (CFR) Sect. 312.33 (2012). Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.33>. Accessed May 9, 2013.

²² FDA guidance *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*.

FDA's expectations on sex-specific patient enrollment, data analysis, and reporting of study information.²³ The guidance recommends that data from such studies be appropriately analyzed for sex differences.

Once marketing applications have been submitted to FDA for review, the Agency uses a variety of tools as part of the product review process to make sure sponsors have met relevant requirements. Examples of FDA reviewer tools include reviewer checklists, review templates, and a variety of internal standard operating procedures (see Appendix 1, Table 3).²⁴

²³ FDA draft *Guidance for Industry and Food and Drug Administration Staff, Evaluation of Sex Differences in Medical Device Clinical Studies*.

²⁴ Reviewer checklists ensure that all relevant sections and information, such as demographic information of participants, are included in an application prior to review. The review templates are structured outlines with an annotated table of contents used in preparing a marketing application review. Review templates aid FDA reviewers in organizing review content for consistency in documentation, using good review practices. FDA standard operating procedures provide reviewers with general operating standards for reviewing product applications and their respective supplements, product labeling, and annual reports. These operating procedures are directed toward FDA staff in the performance of their daily activities.

Part 1: Drugs and Biologics

A. Introduction

This section reports on the following with regard to drugs and biologics:

- The extent to which these applications include demographic data subset analyses on age, sex, and race/ethnicity population categories (subset analysis) The extent to which demographic subgroups are represented in clinical trials
- The public availability of a summary of product safety and effectiveness data by demographic subgroups and the timeliness of availability

This section discusses new molecular entity drugs and new biologic licensing applications approved in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) during 2011. During this time period, 35 new drugs and biologics were approved or licensed for 36 new indications (*indication* is the approved use).²⁵

A list of the 31 indications (24 drug indications and 7 biologics indications) approved in CDER that were reviewed for this report is provided in Appendix 2.

The five biologics applications approved in CBER that were reviewed for this report were for the following indications:

- For use in military populations 17 through 50 years of age for active immunization for the prevention of febrile acute respiratory disease caused by Adenovirus Type 4 and Type 7 (*prophylactic vaccine*)
- For the routine prophylactic treatment of Congenital Factor XIII deficiency (*orphan designation*)
- For the treatment of clinical signs of scorpion envenomation (*orphan designation*)
- For improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults²⁶
- For the detection of delayed-type hypersensitivity to *C. immitis* in individuals 18–64 years of age with a history of pulmonary coccidioidomycosis (*orphan designation*)

The working group evaluated marketing applications submitted to FDA, clinical review documents, approved product labeling (package inserts), and other documents on FDA's web site to determine the extent to which demographic information was collected, analyzed, and included

²⁵ One product was approved for 2 different indications.

²⁶ This is an *autologous* product (i.e., derived using the patient's own cells).

in the sponsors' marketing applications to FDA and made publicly available once an application was approved.

The demographic categories used in Part 1 include age, sex, race, and ethnicity, defined as:

Age: Pediatrics (age ≤ 16 years), geriatrics (age ≥ 65 years)²⁷

Sex: Male, female

Race: White, Black or African-American, Asian, American Indian or Alaska Native,* Native Hawaiian or Other Pacific Islander.*

*Since the percentages of these categories were low for each of the drug and biologics applications, they were summarized together in this report.

Ethnicity: Defined as Hispanic or Latino or not.

Note on Ethnicity: Although ethnicity was addressed in many of the documents, for drugs and biologics approved in CDER, it was not analyzed for this report. This is because some applications reported race and ethnicity as one item, rather than separately (no requirement exists for sponsors to collect these data separately).²⁸ The largest ethnic group defined was Hispanic. However, in some applications, the population was further defined as subpopulations and in others, it was not. Absence of ethnic distinctions in an application does not necessarily mean that Hispanic/Latino or other ethnic groups of patients were not studied; rather, these patients were categorized by their race, not their ethnicity. The Office of Management and Budget (OMB) acknowledges that the categories in this classification are social-political constructs and should not be interpreted as being scientific or anthropological in nature.²⁹

B. Demographic Subgroup Information Contained in Applications

The following discussion presents the findings in more detail, with accompanying graphic representations of the demographic data reported and analyzed, first for applications approved in CDER, then for applications approved in CBER.

²⁷ According to 21 CFR 201.57(f)(9)(i), the pediatric age group is defined as "birth to 16 years, including age groups often called neonates, infants, children, and adolescents." FDA states in guidance, however, that the Best Pharmaceuticals for Children Act (BPCA) defines *pediatric studies* to include studies in "all pediatric age groups including neonates in appropriate cases, in which a drug is anticipated to be used." For the purposes of satisfying the requirements of the Pediatric Research Equity Act (PREA), the appropriate age ranges to be studied may vary, depending on the pharmacology of the medical product, the manifestations for the disease in various age groups, and the ability to measure the response to therapy. In general, however, the pediatric population includes patients aged "birth to 16 years, including age groups often called neonates, infants, children, and adolescents."

²⁸ Sponsors interested in collecting ethnicity and race separately can follow the recommendations for doing so in FDA guidance (i.e., *Collection of Race and Ethnicity Data in Clinical Trials*).

²⁹ Office of Management and Budget, Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Available at www.Whitehouse.gov/omb/fedreg_1997standards/ Accessed March 12, 2013.

Findings for Applications Approved in CDER

For the drug and biologics applications approved in CDER in 2011, the working group collected data from the key clinical studies, identified from approved product labeling as those studies that provide evidence of efficacy, safety, and benefit–risk to support FDA’s approval decisions. These studies, sometimes referred to as *pivotal trials*, are clinical investigations designed to collect definitive evidence of the safety and effectiveness of a medical product for a specified intended use, typically in a statistically justified number of patients.

The working group found that all of the applications approved in CDER provided information on the demographic composition of the clinical trials. The applications also addressed demographic subset analyses in the summaries of safety and/or efficacy, except for one small study of a product to treat a rare disease. For this one exception, FDA determined that the analysis for a study of fewer than 60 patients with a rare disease was unnecessary, given that the number of patients was too small for subgroup analysis. For the remaining applications, when the number of patients in a demographic category was sufficient for subset analysis, data were presented in the application. Detailed information with graphs of this analysis is found in Section C below.

1. CDER – Age Composition

All of the applications approved in CDER and evaluated by the working group reported age composition (geriatrics and pediatrics).

- Geriatrics

Overall, the findings showed that the percentage of geriatric patients participating in clinical studies varied by indication and tended to reflect the prevalence of the disease in the geriatric population. For example, acute lymphoblastic leukemia (ALL), Hodgkin’s lymphoma, Lennox-Gastaut syndrome (a form of childhood-onset seizure disorder), and systemic lupus erythematosus (SLE) occur more commonly in younger patients; thus, geriatric representation would be expected to be low in these clinical studies. Conversely, age-related macular degeneration (AMD) is a disease that occurs predominantly in older people, and the percentage of geriatric patients participating in AMD clinical studies would be expected to be high.

Figure 1-1 shows the results for clinical trial demographic composition by geriatric age. In this figure, the percentage of trial participants who were 65 years or older is plotted according to the product indication. This approach was taken because product indication is often highly relevant to the composition of patients participating in the clinical studies.

Figure 1-1: Trial Composition – Geriatrics

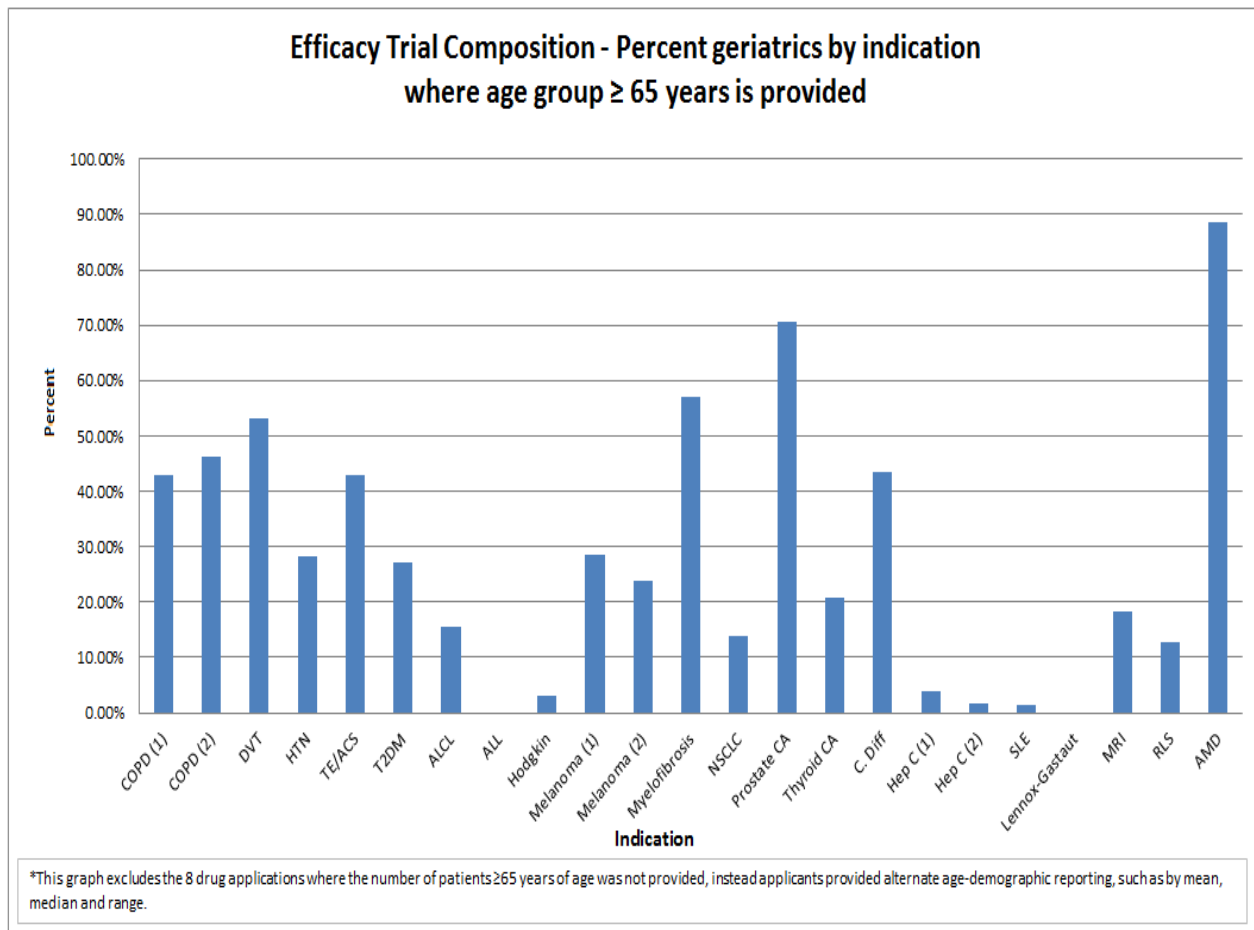


Figure 1-1 Abbreviations: COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; HTN = hypertension; TE/ACS = thrombotic events in acute coronary syndrome; T2DM = type 2 diabetes mellitus; ALCL=anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; Hodgkin = Hodgkin’s lymphoma; NSCLC = anaplastic lymphoma kinase-positive non-small cell lung cancer; Prostate CA = prostate cancer; Thyroid CA = medullary thyroid cancer; C. Diff = *Clostridium difficile*-associated diarrhea; Hep C = hepatitis C; SLE = systemic lupus erythematosus; MRI = intravenous use in diagnostic magnetic resonance imaging; RLS = restless leg syndrome; AMD = age-related macular degeneration

Note: The geriatric data graph excludes eight drugs and biologics – even though the documents for them did include age information – because the application summaries provided age information as a median with range (e.g., median age 60 with a range of 40 to 87 years) or used an age grouping different from ≥65 years (e.g., ≥60 years), and the percentage of patients ≥65 years could not be found.

- Pediatrics

Pediatric demographic composition graphs were not generated because only three of the drugs and biologics were studied in pediatric patients. The small number of pediatric patients studied is an expected finding because half of the drugs and biologics have an indication that rarely or never occurs in children (e.g., age-related macular degeneration). In addition, new drugs and biologics,

like those reviewed for this report, are generally studied first in adults before exposing children to unknown risks. The Pediatric Research Equity Act (PREA)³⁰ may require additional study in children in the postmarket period. For 12 of the applications reviewed for this report, additional postmarket studies in children were identified in the product approval letters as studies to be submitted as supplements to the original application (approval letters are publicly available on Drugs@FDA).³¹

2. CDER – Sex Composition

All of the applications approved in CDER during 2011 and examined for this report reported trial composition by sex. Overall, and similar to the findings by age, the percentage of patients by sex who participated in clinical studies tended to reflect the prevalence of the disease in men and women. For example, there was no female representation in the prostate cancer trial, whereas SLE, which is predominantly a disorder of women, had a high percentage of female participants. Figure 1-2 shows the results for clinical trial demographic composition by female sex, plotted according to the drug or biologics' indication.

³⁰ Pediatric Research Equity Act of 2003. Public Law No 108-155 (December 3, 2003). Available at <http://www.gpo.gov/fdsys/pkg/PLAW-108publ155/html/PLAW-108publ155.htm>. Accessed November 29, 2012.

³¹ Drugs@FDA. Available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed November 28, 2012.

Figure 1-2: Trial Composition – Sex

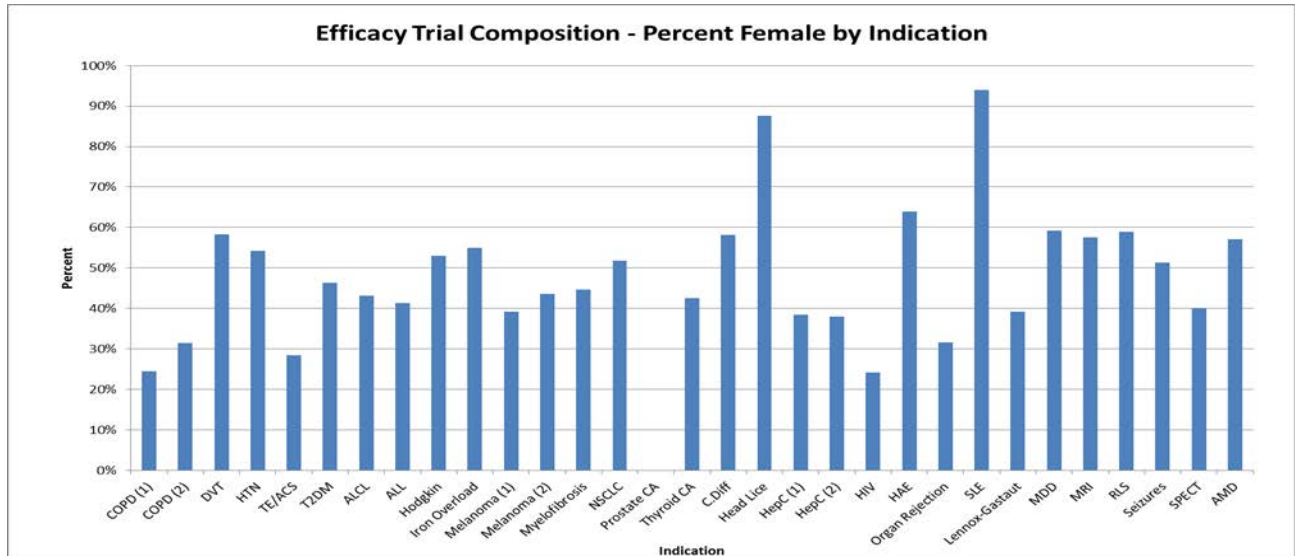


Figure 1-2 Abbreviations: COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; HTN = hypertension; TE/ACS = thrombotic events in acute coronary syndrome; T2DM = type 2 diabetes mellitus; ALCL=anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; Hodgkin = Hodgkin’s lymphoma; iron overload = transfusional iron overload; NSCLC = anaplastic lymphoma kinase-positive non-small cell lung cancer; Prostate CA = prostate cancer; Thyroid CA = medullary thyroid cancer; C. Diff = *Clostridium difficile*-associated diarrhea; Hep C = hepatitis C; HIV = human immunodeficiency virus; HAE = hereditary angioedema; MDD = major depressive disorder; SLE = systemic lupus erythematosus; MRI = intravenous use in diagnostic magnetic resonance imaging; RLS = restless leg syndrome; SPECT = single photon emission computed tomography imaging for Parkinsonian syndromes; AMD = age-related macular degeneration

3. CDER – Race Composition

All of the applications approved in CDER and examined for this analysis reported trial composition by race. The overall findings showed that Whites represented a high percentage of trial participants, which may in part reflect lower percentages of non-White racial demographic subgroups in the U.S. population (see Appendix 3). For some of the indications, race composition in the trials was consistent with the disease prevalence (e.g., melanoma and head lice are more prevalent in Whites). However, for other indications, race composition was not consistent with disease prevalence in the U.S. population, and African American representation was low relative to the African American population with the disease. For example, for type 2 diabetes mellitus (T2DM), African American representation in clinical studies was less than 5%, even though African Americans make up approximately 13% of the U.S. population and have a higher prevalence of T2DM.^{32,33}

³² See Appendix 3 for U.S. Census Bureau 2011 statistics on *People Quick Facts* for the percentage of U.S. population by race.

Table 1-3 shows the results for clinical trial demographic composition by race presented by the percentage of trial participants who were White, African-American, Asian or Other, according to the drug or biologic indication.

³³ U.S. Department of Health and Human Services, Office of Minority Health. Diabetes and African Americans.. Available at <http://minorityhealth.hhs.gov/templates/content.aspx?ID=3017>. Accessed April 4, 2013.

Table 1-3: Trial Composition - Race

Indication	White	Black/African American	Asian	Other
COPD (1)	84%	2%	11%	3%
COPD (2)	87%	2%	7%	4%
DVT	86%	1%	7%	5%
HTN	70%	19%	2%	9%
TE/ACS	92%	1%	6%	1%
T2DM	67%	2%	31%	0%
ALCL	83%	12%	2%	3%
ALL	78%	10%	2%	10%
Hodgkin	87%	5%	7%	1%
Iron Overload	73%	1%	17%	8%
Melanoma (1)	99%	1%	0%	0%
Melanoma (2)	100%	0%	0%	0%
Myelofibrosis	88%	2%	2%	8%
NSCLC	63%	3%	30%	4%
Prostate CA	93%	4%	2%	2%
Thyroid CA	95%	1%	3%	2%
C.Diff	90%	9%	1%	0%
Head Lice	92%	0%	2%	6%
HepC (1)	83%	14%	2%	2%
HepC (2)	87%	9%	2%	3%
HIV	61%	23%	13%	3%
HAE	94%	0%	0%	6%
Organ Rejection	67%	11%	8%	15%
SLE	52%	12%	17%	19%
Lennox-Gastaut	67%	11%	20%	2%
MDD	81%	14%	2%	3%
MRI	46%	5%	45%	3%
RLS	95%	2%	1%	2%
Seizures	92%	3%	1%	4%
SPECT	99%	1%	0%	0%
AMD	85%	0%	11%	4%

Table 1-3 Abbreviations: COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; HTN = hypertension; TE/ACS = thrombotic events in acute coronary syndrome; T2DM = type 2 diabetes mellitus; ALCL=anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; Hodgkin = Hodgkin’s lymphoma; iron overload = transfusional iron overload; NSCLC = anaplastic lymphoma kinase-positive non-small cell lung cancer; Prostate CA = prostate cancer; Thyroid CA = medullary thyroid cancer; C. Diff = *Clostridium difficile*-associated diarrhea; Hep C = hepatitis C; HIV = human immunodeficiency virus; HAE = hereditary angioedema; SLE = systemic lupus erythematosus; MDD = major depressive disorder; MRI = intravenous use in diagnostic magnetic resonance imaging; RLS = restless leg syndrome; SPECT = single photon emission computed tomography imaging for Parkinsonian syndromes; AMD = age-related macular degeneration

Findings for Applications Approved in CBER

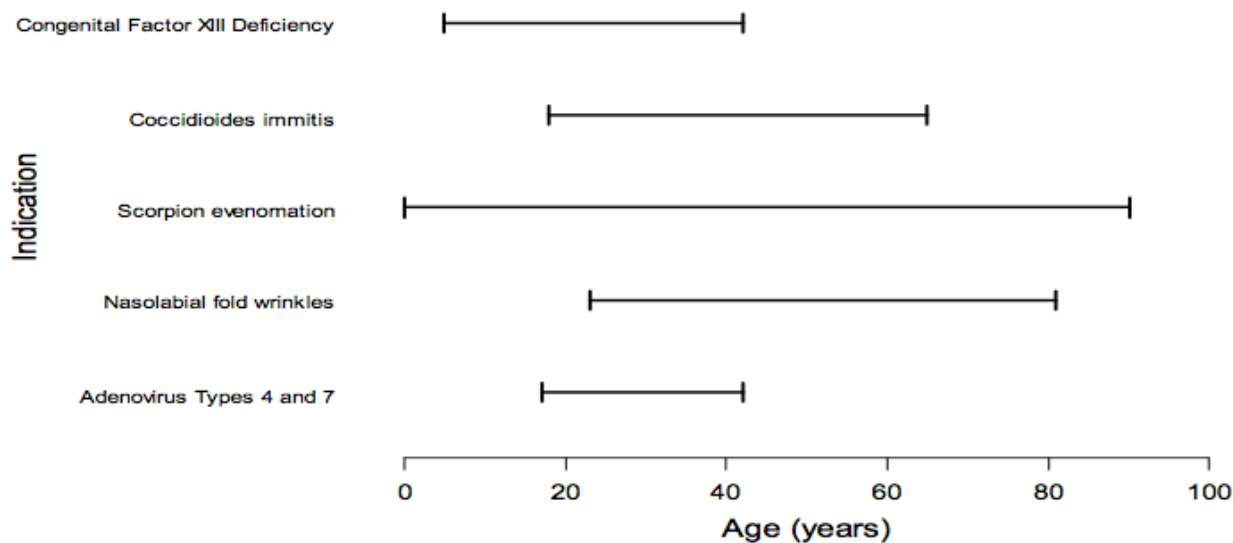
For the five biologics applications reviewed, the working group collected data from the approved product labeling and the clinical reviews. The working group found that all of the applications approved in CBER provided information on the demographic composition of the clinical trials, including the number of subjects, age, sex, and race for the pivotal studies to support approval of their products.

When viewing the graphic representations that follow, it is important to note that for orphan products, the sample sizes are relatively small³⁴ so representations of different subgroups on the graph may appear large but, in fact, may only differ by one or two patients.

4. CBER – Age Composition

In all five applications, the ranges of the participant ages were reported. Pediatric patients were enrolled in studies in three of the applications, and geriatric patients were enrolled in studies in two. Figure 1-4 shows the age range by indication for the applications approved in CBER.

Figure 1-4: Age Range by Submission (CBER)-Efficacy Trial Composition



³⁴ The Orphan Drug Act defines a *rare disease* as a disease or condition that affects fewer than 200,000 persons in the United States. Orphan Drug Act, Public Law No 97-414. Available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/OrphanDrugAct/default.htm>. Accessed April 4, 2013.

Two applications subject to PREA received full pediatric study waivers, so studies in the pediatric subpopulations are not required. Full waivers are granted in many cases when the disease or condition is not likely to occur in the pediatric population. For example, for the prophylactic vaccine, which is indicated for the military population, it is expected that pediatric and geriatric subgroups would not have been enrolled. This is reflected in the product labeling, and the age ranges are stated in the indication and labeling where appropriate. The remaining three applications were not subject to PREA due to orphan designation; however, two included pediatric patients in the study cohort, as noted in Figure 1-4, since the disease occurs in the pediatric population.

When significant safety concerns or insufficient data exist for certain subpopulations, this information is made available in the appropriate section (i.e., 8.4 Pediatric Use or 8.5 Geriatric Use) of the product labeling. For example, for the biologic indicated for the improved appearance of nasolabial fold wrinkles, the label states under the heading, **8.5 Geriatric Use:**

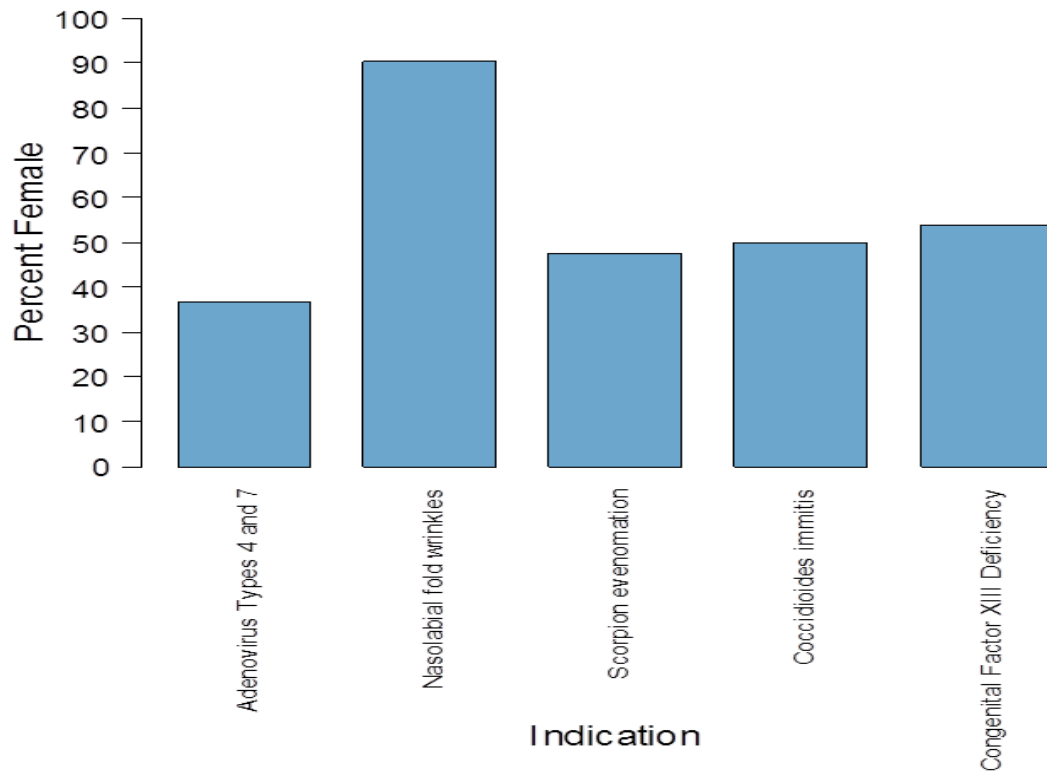
Clinical studies ... did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. [See Clinical Studies (14)].

Additionally, when outcomes are analyzed by age, these are stated in the label. The following language is present in two different product labels, both of which are orphan products: "*There were no apparent differences in the safety profile in children as compared to adults*" and "*The efficacy and safety ... is comparable in pediatrics and adult patients.*"

5. CBER – Sex Composition

All five applications approved in CBER described trial populations by sex (Figure 1-5). For the nasolabial fold wrinkle indication, more than 90% of the studied population was female. In the remainder of the studies, the percentage of participants was generally evenly distributed between male and female participants.

Figure 1-5: Sex Composition by Submission (CBER)-Efficacy Trial Composition



6. CBER – Race Composition

All five applications approved in CBER during 2011 provided racial and/or ethnicity data. Although a large percentage of the enrolled patients were White, this was not always the case. White participants comprised the majority of all racial subgroups enrolled for four of the five applications. For one orphan product, African American or Black patients made up the highest percentage among the racial subgroups enrolled.

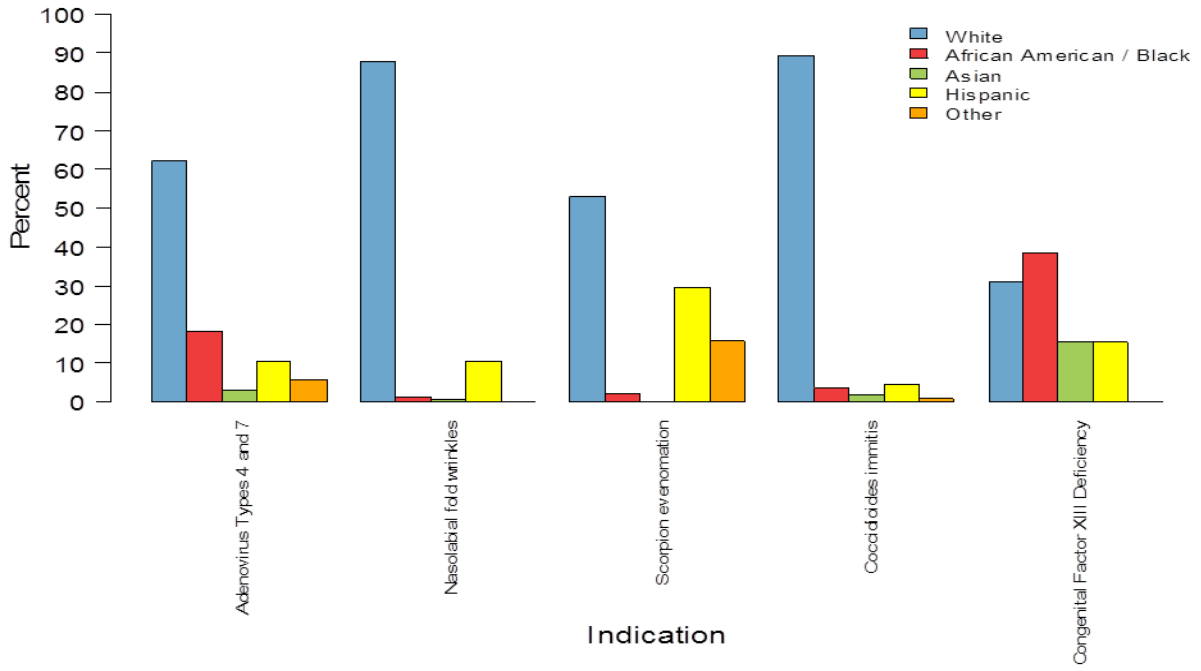
In the application for a nasolabial fold wrinkle indication, the percentage of Whites exceeded 90%, and the labeling reflects the race composition. The labeling under the heading, **8.6 Race**, states:

Clinical studies ... did not include sufficient numbers of subjects in non-White populations to determine whether they respond differently from the population studied.

The racial and ethnic study population enrollment can also be influenced by geographic distribution of the disease (e.g., scorpion envenomation). The population enrollment also can be influenced by the indication and target population. For example, in the product for prevention of respiratory disease caused by adenovirus types 4 and 7 for the military population, approximately 18%, or almost one fifth of the subjects enrolled were African American, which is representative of the U.S. military population³⁵ (see Figure 1-6).

³⁵ United States Department of Defense. Remembering the Legacy, African Americans in the Military. Available at <http://www.defense.gov/home/features/2007/blackhistorymonth/index.html> Accessed April 4, 2013.

Figure 1-6: Racial/Ethnic Composition by Submission (CBER)-Efficacy Trial Composition



C. Subset Analyses in Applications and Public Availability of Data

Findings for Applications Approved in CDER

Drug and biologics applications are reviewed by CDER scientists and their reviews are publicly available on FDA's Web site (i.e., posted on Drugs@FDA) if the new drug or biologic is approved for marketing. Labeling is likewise posted for approved drugs and biologics. FDA approved *labeling* refers to the official description of a drug or biologic and includes information on how the drug or biologic should be prescribed (e.g., dose, indication, patient population), side effects and safety information, and instructions for use. The labeling also includes summary results of the key clinical studies (evidence of effectiveness) that supported drug or biologic approval.

The working group examined labeling posted on Drugs@FDA for demographic subset analyses of effectiveness and safety, including clinical pharmacology (clinical pharmacology addresses how drugs and biologics are metabolized by the body, drug interactions, and other information). If the information was not found in the labeling, the FDA medical officer, biostatistician, and/or clinical pharmacologist reviews were consulted. The rationale for this approach was that all information in labeling underwent review (and would, therefore, appear in FDA reviews), but reviews would also contain additional information that was not included in labeling. This is because FDA-approved product labeling is designed to communicate information important to the safe and effective use of the product, not to provide a comprehensive catalogue of all available information.

For each demographic category (age, sex, and race), we asked two questions for this report about each subset analysis (safety, efficacy, clinical pharmacology):

1. Does a public document *address* demographics? This question was answered "no" if no mention of the topic was found (e.g., no mention of subset analysis of safety by age).
2. Does a public document contain *data* about subset analysis for each of the demographic categories? This question was answered 'no' if the document stated that representation by a demographic category was too low for meaningful analysis, or similar explanation (e.g., if a small trial had only a few percent non-White participants, the answer to this question was "no data").

Publicly available documents on Drugs@FDA (labeling and/or reviews) provided demographic information for all of the CDER-approved drugs and biologics examined for this report. Information included the demographic composition of trials, and, when sufficient demographic subset numbers were enrolled, subset information was provided. The following sections and figures show the subset information for each of the demographic categories (age, sex, and race), including whether the information was found in labeling, one or more reviews, or both.

1. CDER–Public Availability of Age Subset Data

Sections on geriatric and pediatric age subset information are required in product labeling³⁶; thus, all of the applications reviewed for this report addressed age subsets in labeling.

- Geriatrics

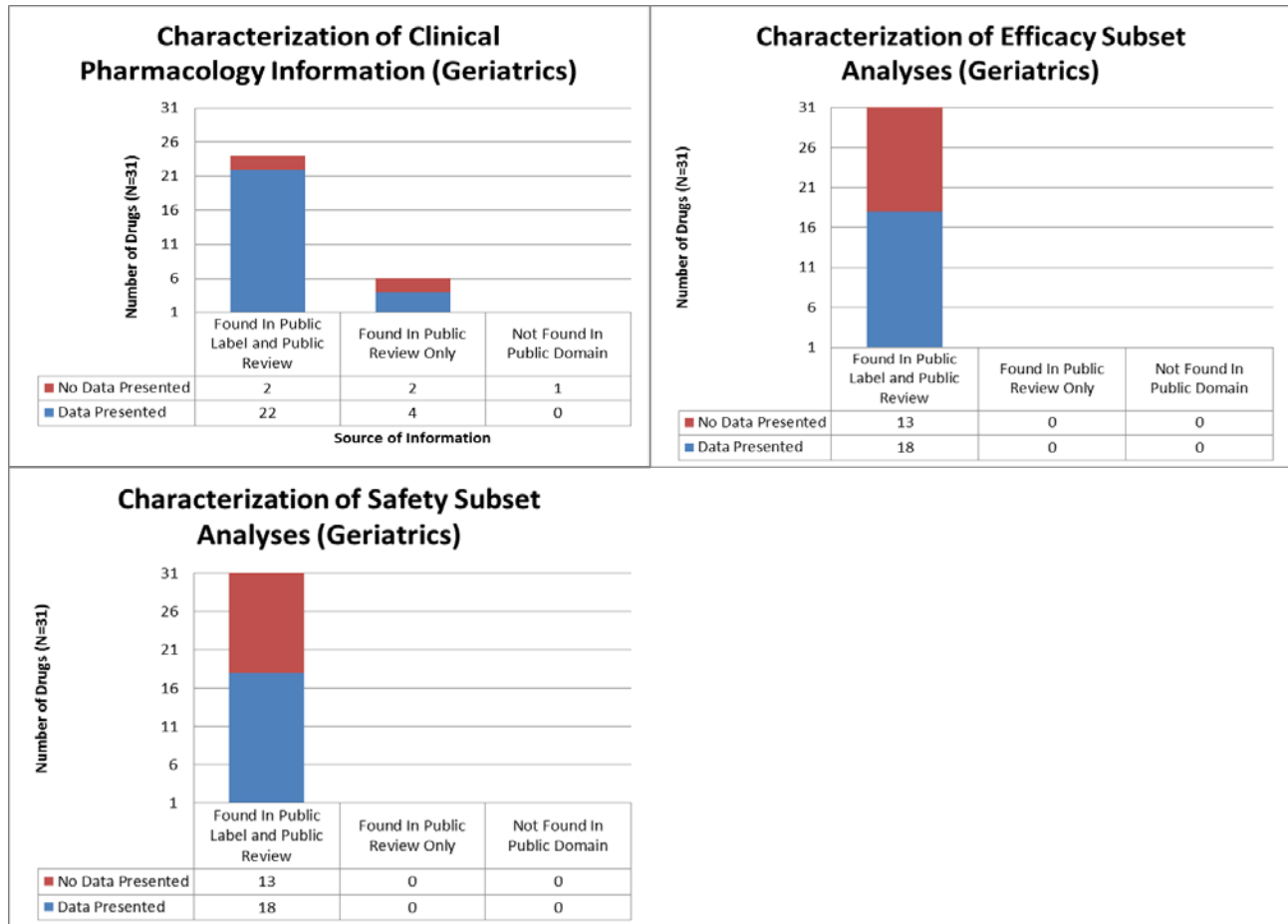
For all of the applications, the age composition of the trials was reported in publicly available documents, and all labeling had required geriatric labeling subsections. Figure 1-7 shows the results for subset analysis by the geriatric age subset. This figure shows whether geriatrics was addressed with data or without data for each type of subset analysis, including clinical pharmacology, efficacy, and safety analyses, as follows:

- The first bar in each graph shows the number of drugs and biologics with publicly available information in labeling *and* at least one FDA review.
- The second bar shows the number of applications that had information in an FDA review, but not in labeling.
- The last bar shows the number (if any) for which no publicly available information was found on Drugs@FDA.
- The sum of all the bars in each graph equals the total number of approved drug and biologic indications in this report (31).

The blue part of each bar indicates the presence of data; the red part indicates that the topic was addressed, but without data (e.g., the Geriatrics labeling subsection would state that few patients ≥ 65 years old were studied). The first graph shows that geriatric clinical pharmacology information was found in labeling and in at least one review for 24 of the 31 indications. For an additional six indications, information was not in labeling, but was found in at least one review. No publicly available information was found for the one remaining application.

³⁶ Requirements on content and format of labeling for human prescription drug and biological products. 21 CFR Section 201.56. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56>. Accessed May 9, 2013.

Figure 1-7: Public Availability of Geriatric Subset Analysis



Note: There were 31 indications for 30 drugs and biologics. In these figures, *drugs* is used to refer to NME drugs and biologics approved or licensed by CDER. When the total number of indications = 31, the graph range begins at 1 rather than 0; on those graphs, 1 appears as the straight line, rather than a bar above the line.

- Pediatrics

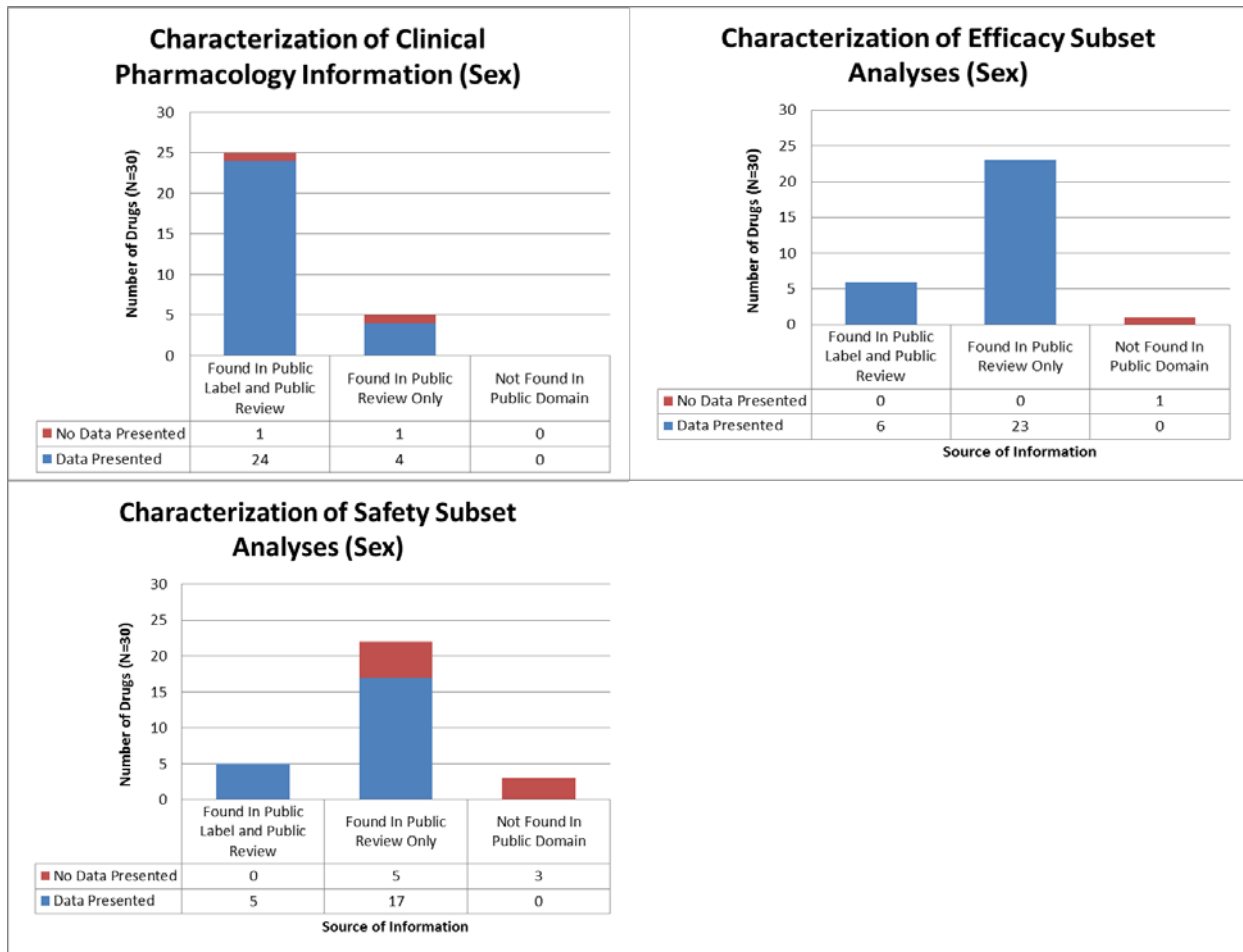
For all of the applications, the age composition of the trials was available in publicly available documents, and all labeling had required pediatric labeling subsections, but most did not contain pediatric clinical data. As was noted earlier, this was an expected finding.

2. CDER–Public Availability of Sex Subset Analysis

For all of the reviewed applications, the sex composition of the key clinical studies was available in publicly available documents and almost all had sex subset analysis data in publicly available documents.

Figure 1-8 shows the results for subset analysis by sex (male or female). This figure is organized exactly as described for the age subset analysis figure, except that the total number of drugs and biologics equals 30 instead of 31 because one product was indicated exclusively for males for the treatment of prostate cancer, and no analysis by sex would have been performed.

Figure 1-8: Public Availability of Sex Subset Analysis



Note: There were 30 indications for 29 drugs and biologics. In the figures, the term *drugs* refers to both NME drugs and biologics approved in CDER. One sex-specific indication was excluded from the analysis.

These graphs show that for most of the reviewed applications, clinical pharmacology sex subset data were included in labeling (24 of 30), but not efficacy and safety subset analyses. However, most had efficacy and safety information in the reviews (thus, for the efficacy and safety graphs,

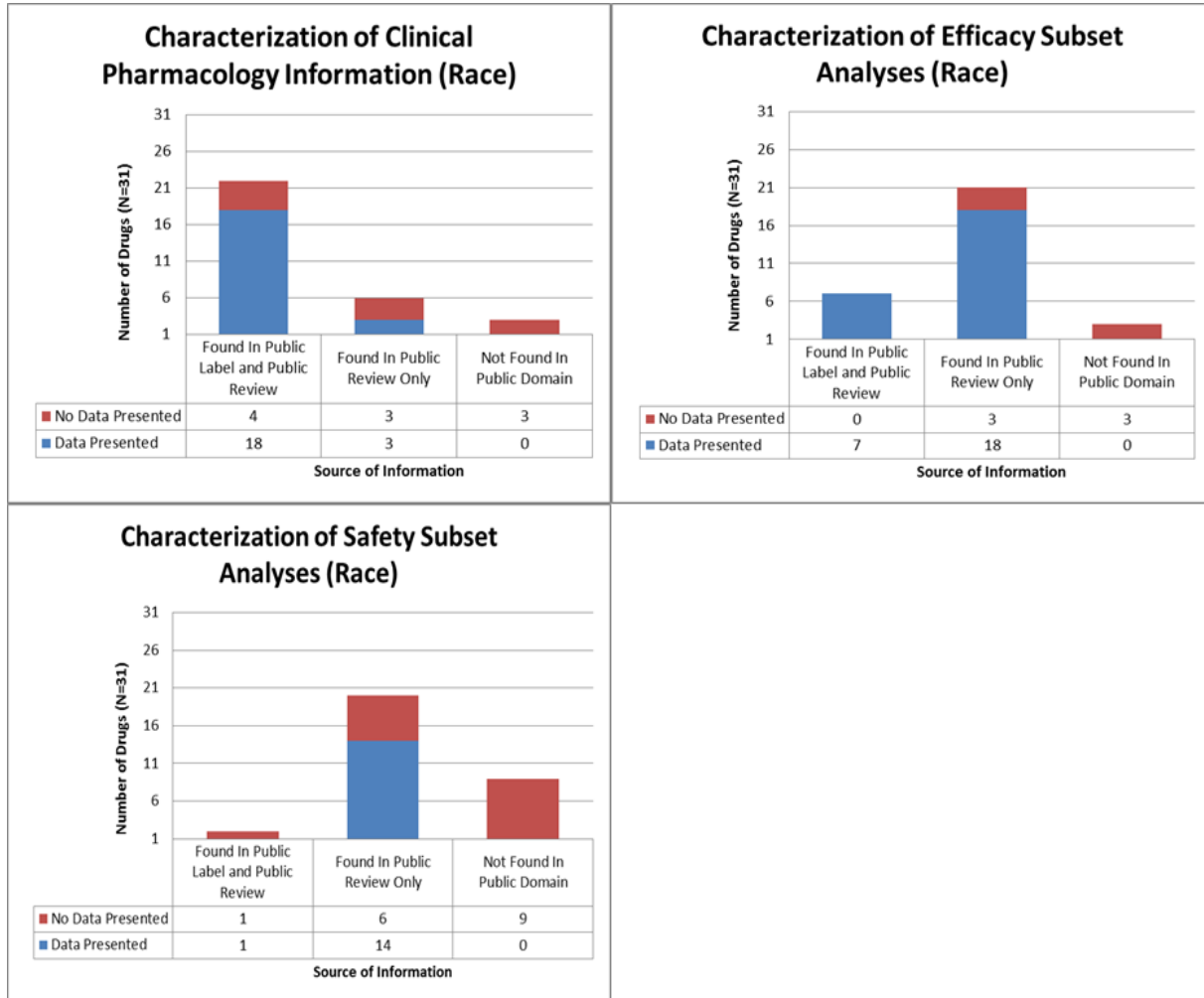
the second bar, review only, is larger than the first bar, review and labeling). In the efficacy graph, adding the two bars (6 + 23) shows that for almost all (29 of 30), sex subset data were in at least one publicly available document.

We expected fewer labels to include sex demographic information compared to pediatrics and geriatrics, which must be addressed in labeling regardless of whether there is informative data (sex demographic labeling is not a required subsection). Thus, inclusion of sex demographic information in labeling is decided on during the review process based on whether the available information would be informative to prescribers. To a large extent, whether it is included depends on whether there are sufficient numbers of males and females for meaningful subset analysis or whether relevant differences based on sex were noted in clinical studies.

3. CDER–Public Availability of Race Subset Analysis

For all of the reviewed applications, race composition of the trials was made publicly available in documents. Race subset analysis data were publicly available for about 50% (safety analysis) and 80% (efficacy and clinical pharmacology) of the products. Figure 1-9 shows the results for subset analysis by race. This figure is organized as described for the age subset analysis figure.

Figure 1-9: Public Availability of Race Subset Analysis



Note: There were 31 indications for 30 drugs and biologics. In the figures, the term *drugs* refers to both NME drugs and biologics approved in CDER. When the total number of indications=31, the graph begins at 1 rather than 0; on those graphs, 1 appears as the straight line rather than a bar above the line.

These graphs show that approximately half of the applications included clinical pharmacology race subset data in labeling (18 of 31), but few had efficacy and safety subset analyses in the labeling. However, most applications had efficacy and safety subset data in the reviews. For example, the efficacy graph shows that most (25 of 31) had efficacy subset data in at least one publicly available document (7 in labeling + 18 in reviews posted on FDA’s Web site). Safety subset data were present for 15 of the 31 indications.

As with sex demographic subset information, it is expected that fewer labels will include race demographic information compared to pediatrics and geriatrics because these are not required sections for labeling. Thus, inclusion of race demographic information in labeling is decided on during the review process, based on whether the available information would be informative to prescribers. To a large extent, this depends on whether sufficient numbers of non-White patients were available for meaningful subset analysis.

An absence of racial subset data is expected for drugs and biologics approved to treat diseases that primarily affect Whites (e.g., head lice infestation is less common in African Americans, as is melanoma). For many of the applications, there were too few African-American or Black patients in the trials to enable meaningful subset analysis (e.g., see prostate cancer in Figure 3).

It is notable that the approval letters for 4 of the 31 indications included a postmarket commitment or requirement related to race: transfusional iron overload (Iron Overload), single photon emission computed tomography imaging for Parkinsonian syndromes (SPECT), SLE, and hepatitis C.

Overall, the findings for the applications approved in CDER and reviewed for this report show that, as expected, FDA reviews address demographics more often than does labeling. This is because labeling is not a comprehensive summation of all available information. Reviews address demographics even when these categories have no effect on safety and/or efficacy, or there is insufficient data to make that determination.

Because FDA reviews are posted on the Internet after a new drug or biologic is approved, the public has access to all of this information. The most efficient way to access this review information is to go to Drugs@FDA, type in the product name, click on Reviews, and then choose the review of choice. For example, if one is interested in demographic differences in metabolism and dosing of a drug or biologic, look at the Clinical Pharmacology review; for demographic subset information, consult the Medical Officer/Clinical reviews or the Biostatistician reviews. These reviews have tables of contents to aid in efficient information access. Ultimately, however, clinically important information is most readily available in the product labeling, which will include a patient-centered Medication Guide, if required, for dissemination of important safe use information to patients. These are accessible at the same site by clicking Medication Guide instead of Reviews.

As this section shows, in some cases, there was no subset analysis of safety and effectiveness data available publicly, either in FDA reviews or product labeling. There were a number of reasons for this. When a product was intended to treat a disease occurring primarily in one subgroup, there were too few patients from other demographic categories for meaningful inclusion in the analysis (e.g., few male patients in a study for a disease that rarely affects men). This also occurred for the rare disease products when the totality of all affected patients precluded subset analysis because the key clinical studies were, by necessity, small (one third of the applications examined for this report were for rare disease indications).

Findings for Applications Approved in CBER

Descriptions of clinical trial populations by age, sex, and race were included in the labeling and/or clinical reviews of the five products, and the information is publicly available. For products labeled for pediatric use, this information is posted according to the pediatric tracking requirements under Food and Drug Administration Amendments Act of 2007 (FDAAA).³⁷ The issue of subset analyses was addressed, but in some applications not all subsets were analyzed; the reasons varied.

For three of the five applications (product for adenovirus Types 4 and 7, detection of *C. immitis*, and scorpion envenomation treatment), when the overall effectiveness reflected an overwhelmingly positive response (e.g., greater than 95% effectiveness), the high rate of effectiveness obviated the necessity of additional subgroup analysis. In one application (nasolabial fold wrinkles), the overwhelming number of subjects were White and female (>90%) and thus subset analysis of other subgroups would not have been meaningful. In one application (for Congenital Factor XIII) for an orphan product, the number of subjects studied was too small for a subgroup analysis to be meaningful (N=13).

FDA regulations³⁸ related to biologics do not require sponsors of new biologics applications to present a summary of safety and effectiveness data by demographic subgroups (age, sex, race), or an analysis of whether modifications of dose or dosage intervals are needed for specific subgroups. Nonetheless, FDA provides recommendations to sponsors through its FDA guidance documents to submit such data (see Appendix 1, Table 2).

³⁷ Food and Drug Administration Amendments Act of 2007. Public Law No.110-85 (September 27, 2007). Available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentsToTheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm>. Accessed April 4, 2013.

³⁸ Biological Products, 21 CFR Part 600. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=600>. Accessed May 9, 2013.

D. Summary of Findings for Part 1: Drugs and Biologics

In summary, the findings based on the review of marketing applications for drugs and biologics submitted to FDA and reviewed for this report were as follows:

- Sponsors collected and analyzed demographic trial composition data and submitted them to FDA in their applications.
- FDA reviewers addressed demographics in their reviews, which are available on FDA's Web site.
- Clinically meaningful demographic subset analysis information was included in approved labeling, which is publicly available at the time the drug or biologic is marketed in the United States.
- The extent to which demographic subgroups were represented in the clinical trials showed that, in general, participation by age and sex tended to reflect the disease indication studied.
- Whites represented a high percentage of trial participants. In many cases, other racial subgroups were underrepresented. Ethnicity data varied in terms of whether ethnicity was captured separately or in combination with race categories, and, although provided consistent with current guidance,³⁹ the data could not be analyzed in a meaningful way for this report.

³⁹ FDA guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products*.

Part 2: Medical Devices

A. Introduction

This section addresses the requirement to analyze and report on the following with regard to medical devices:

- The extent to which these applications include demographic data subset analyses on age, sex, and race/ethnicity population categories (subset analysis)
- The extent to which demographic subgroups are represented in clinical trials
- The public availability of a summary of product safety and effectiveness data by demographic subgroups and the timeliness of availability

The working group evaluated original premarket approval (PMA) applications for medical devices (including diagnostic devices) approved in 2011 in FDA's CDRH. PMA supplement applications used to obtain approval for changes or modifications to an approved device were not included in this assessment.⁴⁰

A total of 37 PMA applications were approved in 2011. These included 46 pivotal clinical studies to support the applications. Six PMAs relied on data used in other PMAs (four PMAs relied on one dataset and two PMAs on another). Thus, 33 PMAs contained *unique study datasets*. The working group counted study populations used by more than one PMA only once for the description of the demographics of study participants. All 37 PMAs were reviewed for the questions about demographic data subset analyses and the communication of these results. A list of the applications for medical devices approved in CDRH that were reviewed for this report is provided in Appendix 4, with their specific indications for use.

The working group evaluated PMA applications, approved product labeling, other documents on FDA's Web site, and other relevant review documents to determine the extent to which sponsors collected, analyzed, and submitted to FDA demographic information. In addition, the working group determined the extent to which demographic information was made publicly available. The demographic categories discussed in this report include age, sex, ethnicity, and race.

⁴⁰ PMA supplements are submitted for review and approval by FDA when there may be a change affecting safety or effectiveness of an already approved device, such as to include a new indication for device use or labeling changes. Additional demographic data from clinical studies may be submitted to FDA in support of these supplemental applications. However, this was beyond the scope of this report because the results are not available at the time of the original marketing application submission.

CDRH uses the following categories for each demographic subgroup:

Age:	Mean Age, Standard Deviation, Median Age, Minimum Age, Maximum Age (pediatric age groups for devices are defined up to, but not including, the twenty-second birthday) ⁴¹
Sex:	Male, Female, Not Stated
Race:	White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Other, Not Stated
Ethnicity:	Hispanic or Latino, or not

The working group reviewed Summaries of Safety and Effectiveness Data (SSEDs),⁴² device labeling, review documentation, and the product applications to extract demographic information. Similar to the approach used for CDER and CBER, CDRH data were collected initially from the publicly available labeling and SSED. When demographic information was not found in public documents, the working group turned to non-public review documentation and the product applications.

Trial composition demographics were recorded for investigational and control groups and for total study participants (the sum of participants in the investigational and control groups). For studies that used a non-active control group (e.g., historical or literature control group), wherein control participants were not evaluated during the same timeframe as the investigational group or in the same study, trial composition demographics were recorded for the investigational device group only.

Demographic subset analyses were recorded if there was: (1) a clear analysis of primary and secondary endpoints comparing the relevant subpopulation (sex, age, ethnicity or race); (2) a presentation of results by sex, age, ethnic, or race subpopulations; or (3) a statement that a subset analysis was done that summarizes the results. Public documents describe subgroups that were or were not represented in the clinical trial to support device approval. A data subset analysis was marked as *Not Applicable* if the device had a sex-, age-, ethnicity-, or race-specific indication. Of the 37 PMA applications, 5 PMAs were approved with sex-specific indications, and 7 were approved with age-specific indications; no applications were approved for race- or ethnicity-specific indications.

⁴¹ FDA *Guidance for Industry and FDA Staff on Premarket Assessment of Pediatric Medical Devices*.

Note: FDA guidance documents are available at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>

⁴² An SSED is an FDA document (typically a version is submitted by the applicant and modified by FDA) that is intended to present a reasoned, objective, and balanced critique of the scientific evidence that served as the basis of the decision to approve or deny the PMA. The SSED shows that there was reasonable assurance of safety and effectiveness for the device as labeled based on the nonclinical and clinical studies described in the PMA. The SSED is a summation of both the positive and negative aspects of the PMA. For more, see <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmission/PremarketApprovalPMA/ucm050289.htm#ssed>. Accessed May 25,2013.

The discussion that follows presents the findings in detail. Case examples of certain device types or indications are presented in more detail to highlight when there may be appropriate or insufficient representation of demographic subgroups or underscore unique aspects of certain clinical studies.

B. Demographic Subgroup Information Contained in Applications

For medical device applications approved in 2011, the working group evaluated the extent to which demographic subgroups, including sex, age, ethnic and racial subgroups, are represented in clinical studies to support medical device approvals and contained in applications. The figures in Part 2 are presented by application (n=33) and *exclude* applications that reference patient populations that are already represented in another application.^{43,44,45} For eight applications, *multiple pivotal studies*, or cohorts, were submitted for each application, with secondary studies conducted to evaluate a specific subpopulation or device model. Because of the distinct purpose of these studies, information from these multiple studies is presented in a separate section of Part 2.

The analysis showed that trial composition varied by product area. In addition to presenting the percentage of representation by each demographic subgroup, the figures below identify the percentage of data not reported for a given study or application.⁴⁶ A number of factors influence the interpretation and clinical relevance of demographic information, including, for example, intended population for use, prevalence of disease, and study sample size.

1. Age Composition

All 33 approved PMA applications containing unique study datasets provided age composition data. Of the 33 approved PMA applications, age range was reported in 29 applications. Figure 2-1 depicts the age range and means (when available) of the clinical study populations presented in the PMA applications. Of the 29 PMA applications that reported age range, eight did not report age means. Figure 2-1 excludes four PMA applications that did not report the age range in all clinical studies; when age range was not provided, other age data were included in the submission (e.g., mean, median, standard deviation, number of subjects by age groups, etc.).

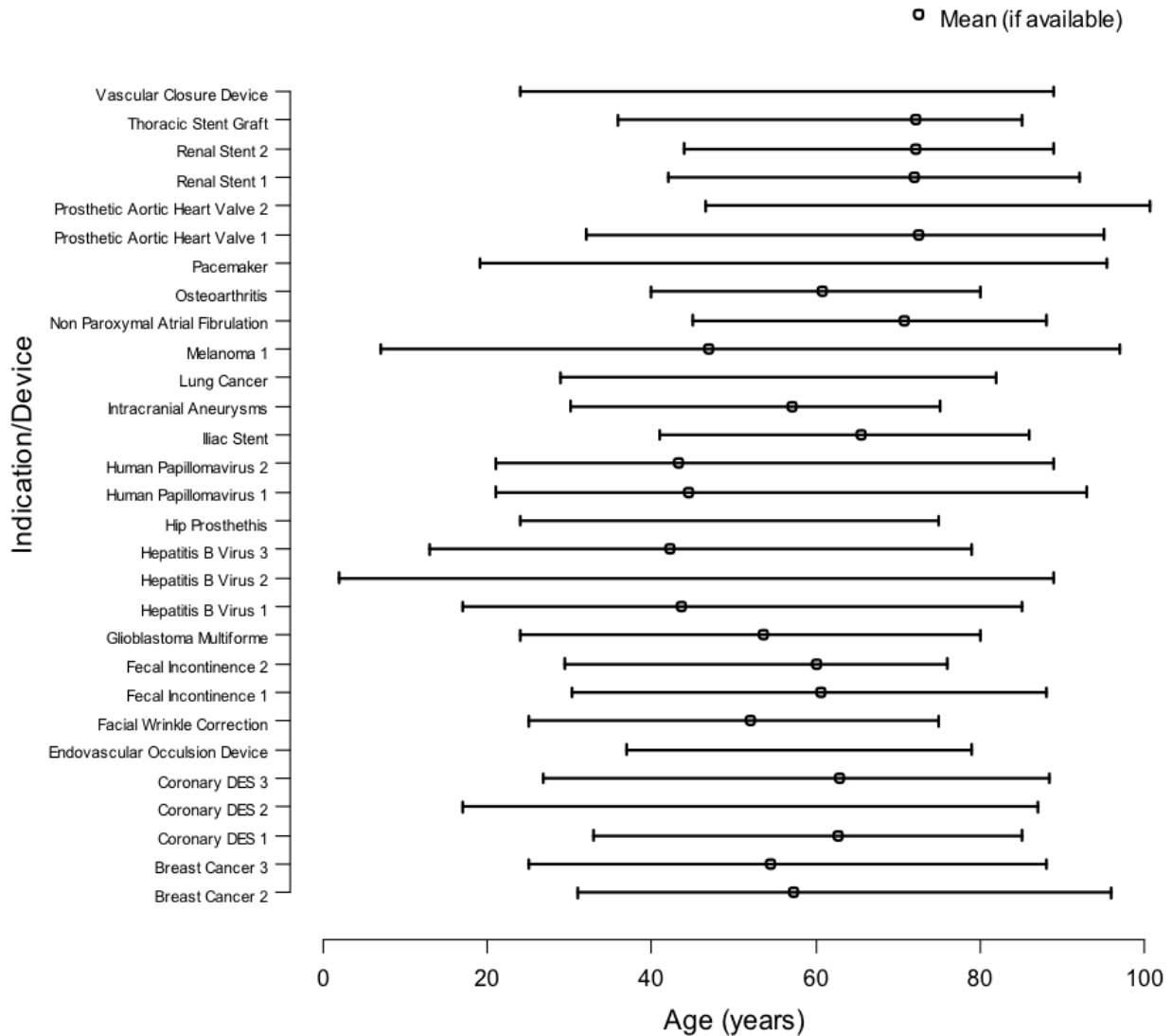
⁴³ Some in vitro diagnostic applications were excluded from the demographic data because they contained the same study participants (e.g., different assays were tested using the same patient samples).

⁴⁴ In one case, an application was submitted for an in vitro diagnostic companion device. No sex, race, or age analyses were conducted for safety and effectiveness endpoints of the in vitro diagnostic companion device. However, sex, race, and age analyses were conducted for the safety and effectiveness of the related drug.

⁴⁵ Appendix 4 contains a full description of indications associated with each PMA application.

⁴⁶ The percentage *not reported* reflects the total proportion of subjects without demographics reported across all the clinical studies included in this analysis for a given PMA application.

Figure 2-1: Age Range by Submission (CDRH)



The age composition shows that, on average, the study populations for all of the PMAs (reporting a mean age) represented adults. For the clinical studies that reported a mean, the mean age for the study populations ranged from approximately 40 to 75 years.

There was a lack of consistency in the type of descriptive statistics on age reported in the PMAs. The data are presented by range in Figure 2-1 because the age range was most commonly reported. The manner in which the age descriptive statistics are presented in a submission may affect data interpretation. FDA provides guidance on developing medical devices for pediatric

population subgroups (e.g., neonates, infants, children, and adolescents).⁴⁷ However, there is no definition for or device guidance on the geriatric population.

FDA currently has several device-related initiatives underway that target the pediatric subpopulation. In 2007, Congress enacted the Pediatric Medical Device Safety and Improvement Act (PMDSIA) as part of the Food and Drug Administration Amendments Act (FDAAA),⁴⁸ which provides that FDA may extrapolate adult effectiveness data or performance data that demonstrate probable benefit (in the instance of humanitarian device exemptions (HDEs)) to support a pediatric indication when the course of the disease or condition in children and the effects of the device are similar to adults. FDA is developing a guidance document to describe how effectiveness data on adults can be used for extrapolation to support a pediatric indication. The PMDSIA does not address extrapolation of adult safety data.

Additionally, PMDSIA amended the FD&C Act by adding, among other things, a section that requires certain medical device applications to include, if readily available, a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure and the number of affected pediatric patients.⁴⁹ In February 2013, FDA published a proposed rule⁵⁰ to amend 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.

In 2011, FDA approved 38 original PMA and panel-track PMA supplements and 3 HDE applications for pediatric use.

2. Sex Composition

All of the approved PMA applications evaluated by the working group addressed trial composition by sex.

Figure 2-2 shows the results for clinical trial demographic composition by female sex, plotted according to indication or device type. There were five PMA applications with clinical studies representing a 100% female population; these five PMAs were approved for testing or screening

⁴⁷ FDA *Guidance for Industry and FDA Staff on Premarket Assessment of Pediatric Medical Devices*.

Note: FDA guidance documents are available at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>

⁴⁸ Pediatric Medical Device Safety and Improvement Act (PMDSIA). Public Law No 110-85 (March 13, 2007). Available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm>. Accessed July 22, 2013

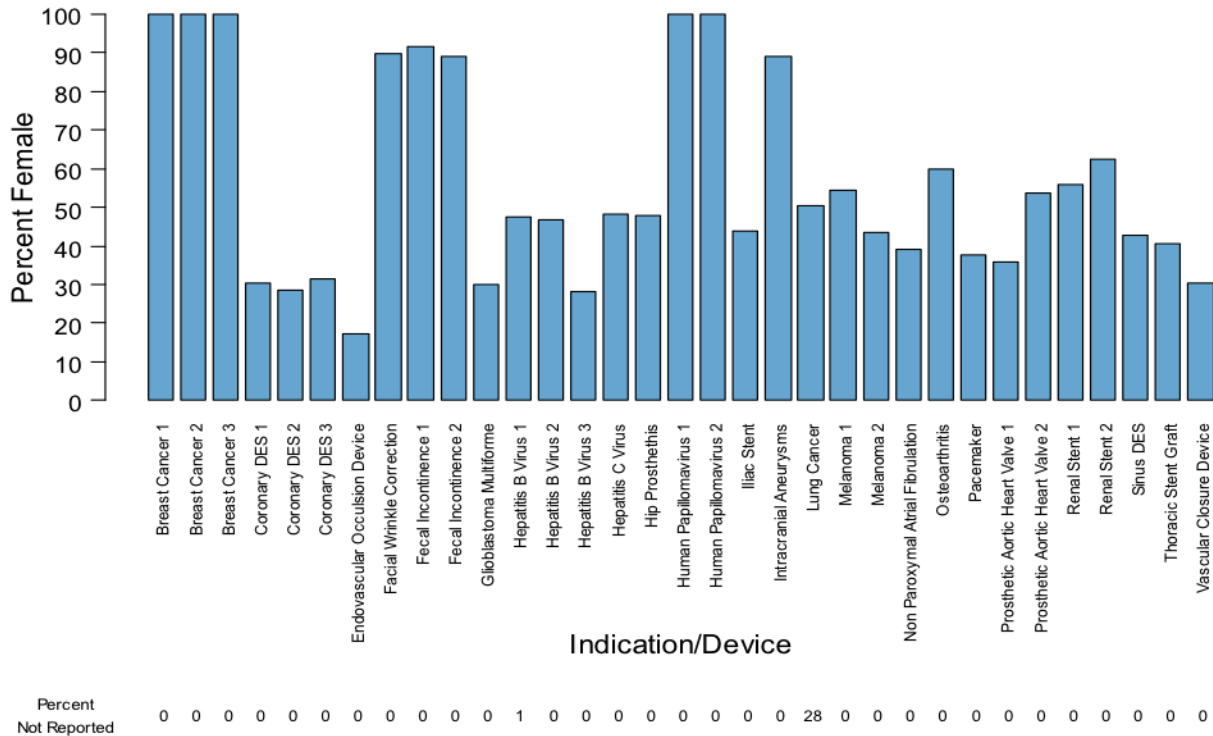
⁴⁹ See Section 515A (21 U.S.C. 360e-1). Available at <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360e-1.htm>. Accessed May 9, 2013.

⁵⁰ The proposed rule is available at <http://www.gpo.gov/fdsys/pkg/FR-2013-02-19/html/2013-03647.htm>. Accessed May 6, 2013.

for breast cancer and HPV in females. The PMAs associated with facial wrinkle correction and fecal incontinence devices included approximately 90% females. A higher percentage of women in the facial wrinkle correction clinical study could potentially be due to the aesthetic indication. Fecal incontinence is slightly more common among women because of the effects of pregnancy and childbirth.⁵¹

The PMA for the endovascular occlusion device had 18% female participation, which is not unexpected for this device type. For devices indicated for use in off-pump beating heart surgery, investigators often select patients with larger coronary size and less diffuse nature of coronary disease, which may lead to a skewed distribution of males and females in the trial patient population when compared to the overall sex distribution of all patients with coronary artery disease.

Figure 2-2: Sex Composition by Submission (CDRH)



⁵¹ National Institutes of Health, 2012. Fecal Incontinence. Publication No. 13-4866, December 2012. Available at <http://digestive.niddk.nih.gov/ddiseases/pubs/fecalincontinence/>. Accessed May 6, 2013.

FDA currently has several device-related efforts ongoing related to sex subgroups. In 2011, FDA issued draft guidance on evaluating sex differences in medical device studies, outlining FDA's expectations on sex-specific patient enrollment, data analysis, and reporting of study information.⁵² The guidance recommends that data from such studies be appropriately analyzed for sex differences. Additionally, in June 2013, CDRH held the Health of Women Public Workshop⁵³ to discuss how to improve the availability, consistency, and communication of sex-specific information for the safe and effective use of medical devices in women; address identified gaps and unmet needs through targeted resources; and foster the development of innovative strategies, technology and clinical study models.

3. Ethnic and Racial Composition

In accordance with FDA's guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials*, issued September 2005,⁵⁴ patients may self-identify in both an ethnic and racial category (e.g., Hispanic-White, Hispanic-Black). In this FDA guidance, OMB "stated that its race and ethnicity categories were not anthropologic or scientifically based designations, but instead were categories that described the sociocultural construct of our society. The Department of Health and Human Services (HHS) chose to adopt these standardized categories for its agencies that report statistics because the categories are relevant to assessing various health related data, including public health surveillance and research." FDA accepts applications containing clinical study data with ethnic and racial demographic data captured as one category or separately. In this section, ethnicity and race data are presented in separate plots and discussed individually.

- Ethnic Composition

Of the 33 approved PMA applications representing unique study datasets evaluated for this report, ethnic demographic data were reported in 23 applications. These data exclude ten PMA applications that did not report any data on ethnic representation. Approximately 46% (21 out of 46) of the pivotal clinical studies that were reviewed collected ethnic demographic data separately from racial data.

Figure 2-3 describes the percentage of Hispanics or Latinos by PMA application. Hispanic or Latino representation ranged from 0.3-35%. The findings indicate that PMAs for hepatitis B virus and HPV have the highest percentages of Hispanics. With the exception of the PMAs for lung cancer detection and for the vascular closure device, ethnicity was reported for the majority of clinical trial participants in the study.

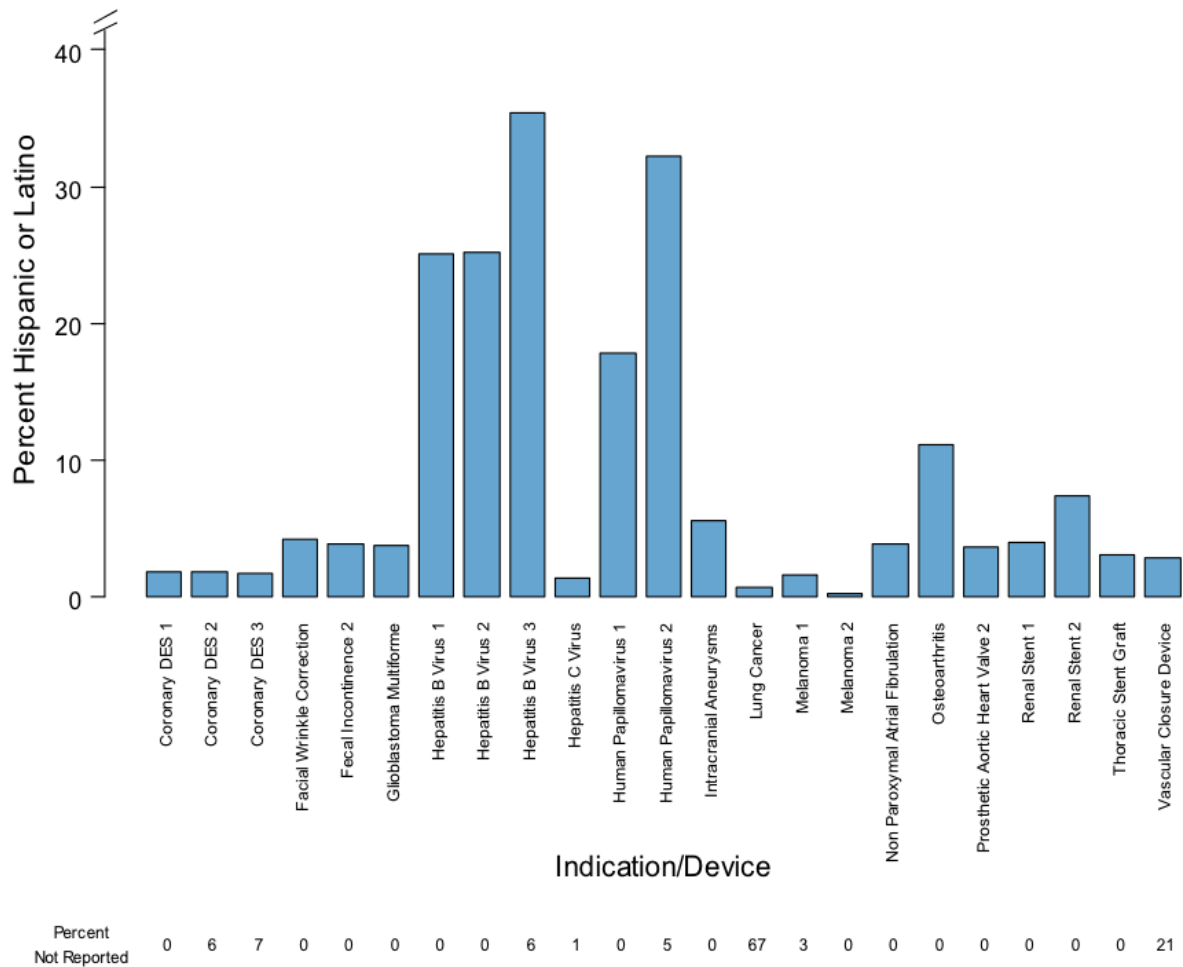
⁵² FDA draft *Guidance for Industry and Food and Drug Administration Staff, Evaluation of Sex Differences in Medical Device Clinical Studies*.

⁵³ See <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346073.htm>

⁵⁴ FDA guidance *Collection of Race and Ethnicity Data in Clinical Trials*.

Note: FDA guidance documents are available at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>.

Figure 2-3: Ethnic Composition by Submission (CDRH)



Note: the y-axis for this graph only goes up to 40%.

- Racial Composition

Of the 33 approved PMA applications containing unique study datasets, race was reported in 23 applications. These data exclude 10 PMA applications that did not report any data on racial composition. Two out of the 10 excluded PMA applications were for in vitro diagnostic devices (IVDDs). IVDD PMA applications often involve clinical studies conducted on specimens not directly obtained from patients as part of the clinical trial (e.g., samples obtained from state laboratories or controlled collections) and may lack accompanying demographic information, as compared to samples taken directly at the patient care setting where demographic information can be obtained.

Figure 2-4 describes the percentage of each racial subgroup in a PMA application sorted by indication or device type. The racial representation illustrates that, in most PMAs, there was a predominant representation of the White population. For three PMAs (hepatitis B virus 2,

hepatitis B virus 3 and facial wrinkle correction device) a relatively high percentage of African Americans or Blacks compared to the other racial subgroups were included. For the facial wrinkle correction device, one of the clinical studies conducted for this PMA assessed the safety and effectiveness of the device specifically in non-White populations.

For some of the indications, racial composition in the trials was consistent with the prevalence of the disease across different racial subgroups when adjusted by the overall population distribution of racial subgroups. For example, African Americans or Blacks have a higher prevalence of infection with hepatitis B⁵⁵ and were similarly observed to have a higher participation in the hepatitis B clinical studies compared to other racial subgroups.

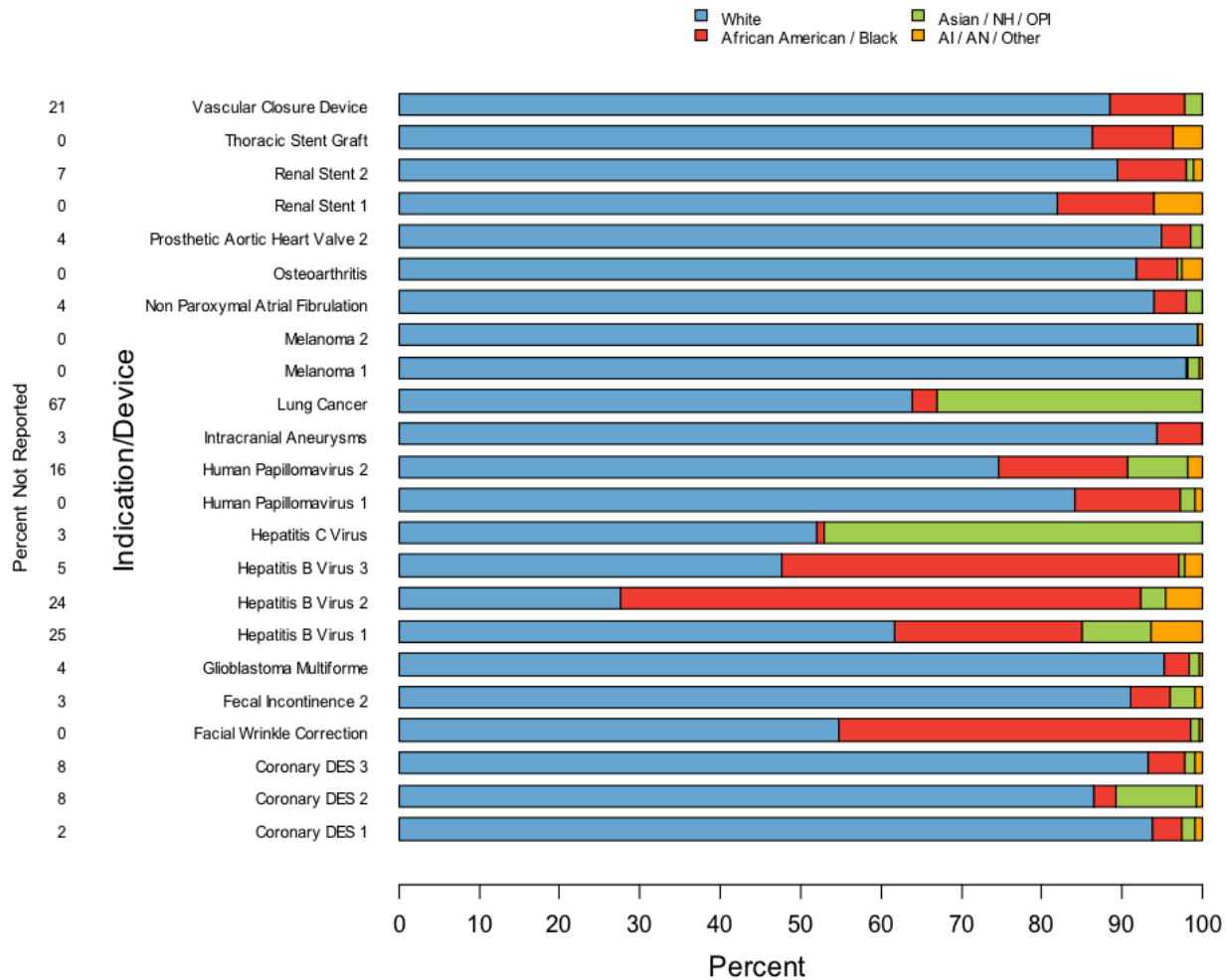
For other indications, racial composition did not appear to represent disease prevalence in the U.S. population. For example, although African Americans have the highest rates for lung cancer⁵⁶ and chronic hepatitis C infection,⁵⁷ this was not reflected in the percentage of African Americans enrolled relative to Whites and Asians/Native Hawaiians/Other Pacific Islanders in the clinical studies for these diseases. In some cases, this could be attributable to the inclusion of foreign study sites (e.g., Asia) in the clinical studies, where African Americans would be less likely to be enrolled.

⁵⁵ Centers for Disease Control and Prevention. 2012. Health Disparities in HIV/AIDS, Viral Hepatitis, STDs, and TB. July 11, 2012. Available at <http://www.cdc.gov/nchhstp/healthdisparities/AfricanAmericans.html#Hepatitis>. Accessed May 6, 2013.

⁵⁶ Centers for Disease Control and Prevention. Lung Cancer Rates by Race and Ethnicity. December 19, 2012. Available at <http://www.cdc.gov/cancer/lung/statistics/race.htm>. Accessed May 6, 2013.

⁵⁷ Centers for Disease Control and Prevention. Hepatitis C in the African American Community. May 21, 2012. Available at <http://www.cdc.gov/hepatitis/populations/AAC-HepC.htm>. Accessed May 6, 2013.

Figure 2-4: Race Composition by Submission (CDRH)



Abbreviations: NH = Native Hawaiian, OPI = Other Pacific Islander, AI = American Indian, AN =Alaska Native

C. Multiple Pivotal Studies

Of the 37 PMAs approved in 2011, 8 were supported by 2 pivotal studies or cohorts. These second pivotal studies were often conducted to evaluate the medical device or diagnostic in a specific subgroup. Consequently, the subgroup demographics of the eight PMAs with multiple studies were assessed separately. Several of the cardiovascular PMAs evaluated the device in the primary study cohort and in patients with smaller blood vessels. In a second example, a facial wrinkle correction device was supported by one study targeting the primary study cohort while another study specifically targeted patients with darker skin pigmentation. Additionally, a product to detect antibodies to the hepatitis e-antigen was evaluated in both the primary and pediatric-study cohorts.

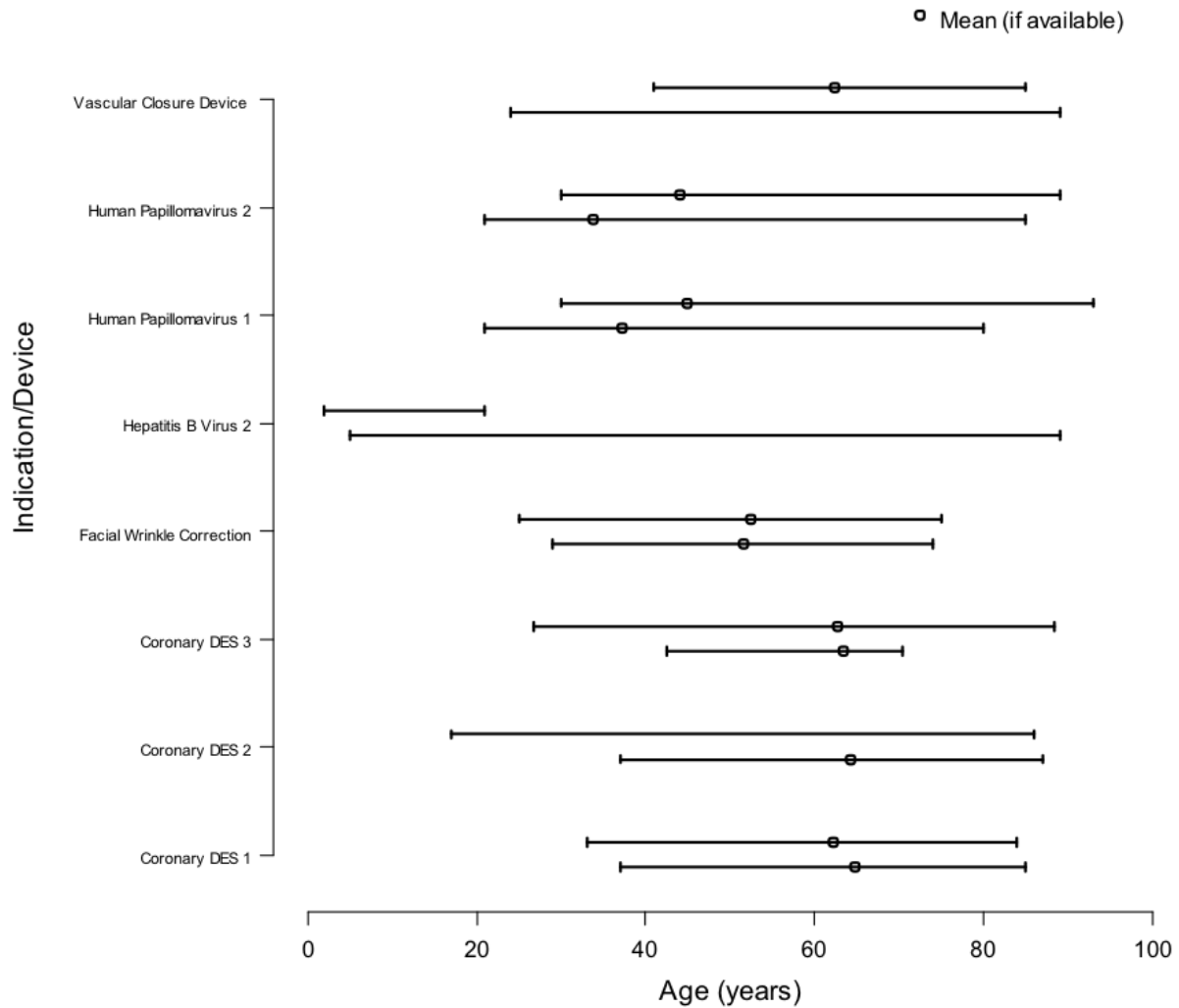
For all eight PMAs with multiple pivotal study cohorts, trial composition was reported for all demographic categories for at least one of the study groups. As previously stated, multiple

factors influence the interpretation and clinical relevance of demographic information, such as intended population for use, prevalence of disease, and study sample size.

1. Age Composition

Figure 2-5 describes the age range and mean age (if available) of the study populations presented by PMA application for PMAs with multiple clinical studies. The results of this age analysis show that, on average, the study populations for PMAs with multiple pivotal studies (where mean age was reported) were adults. For the pivotal studies that reported a mean, the mean ranged from 35 to 65 years old. Figure 2-5 highlights the pediatric subpopulation presented in the hepatitis B virus 2 PMA. As described earlier, inconsistent descriptive statistics were provided for age data in these PMAs. The data are presented by range because the PMAs most commonly reported the age range.

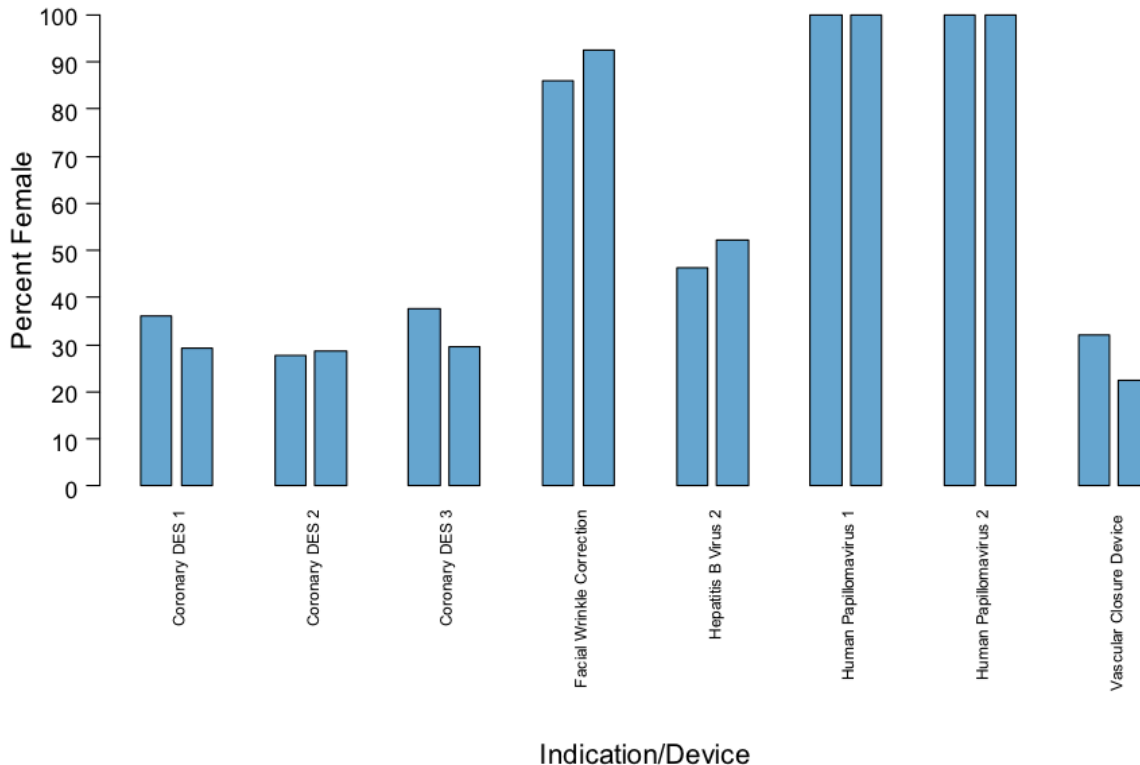
Figure 2-5: Age Range by Study for Submissions with Two Studies (CDRH)



2. Sex Composition

Figure 2-6 describes the female sex composition data presented by study for PMAs with two pivotal studies. As described previously, the facial wrinkle correction PMA consisted of two pivotal studies evaluating the safety and effectiveness of the device in the primary study cohort and in a specific racial subgroup. Both pivotal studies for this PMA had a high representation of females (approximately 85 and 95%). The HPV clinical studies enrolled only females.

Figure 2-6: Sex composition by Study for Submissions with Two Studies (CDRH)



3. Ethnic and Racial Composition

In this section, race and ethnicity data are presented in separate plots and discussed individually.

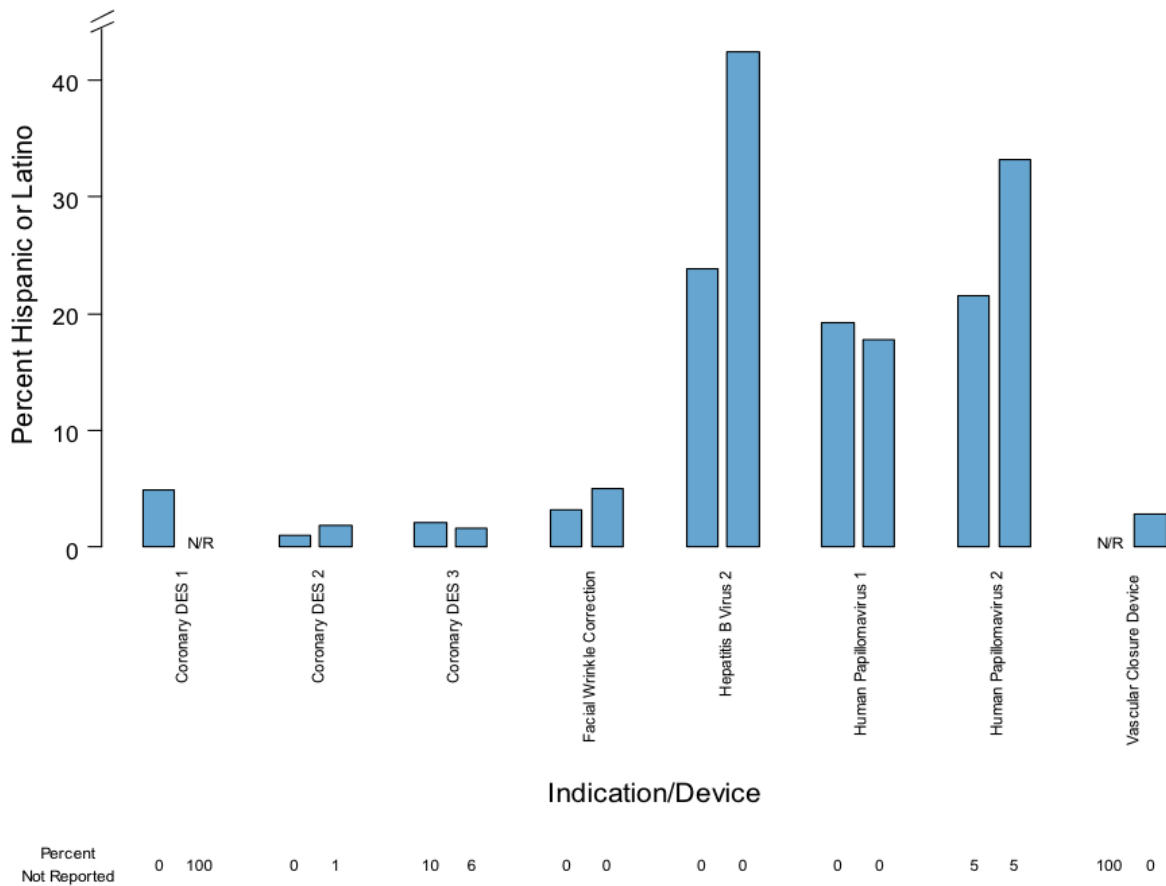
- Ethnic Composition

Figure 2-7 describes the percentage of Hispanics or Latinos by PMA for PMA applications with multiple pivotal studies. For two PMAs (coronary drug eluting stent 1 and vascular closure device), the ethnic composition for one of the study cohorts was not reported. There was generally a low representation of Hispanics across the eight PMAs with multiple studies, with the exception of the hepatitis B virus 2 PMA, in which the pediatric clinical study had more than 40% Hispanic representation (see Case Example), and both HPV PMAs, which had Hispanic representation ranging from approximately 20–35%. Two pivotal studies were conducted for both HPV PMAs because of the indications specifically sought/approved in the PMAs (i.e., one clinical study enrolled women ≥ 21 years of age while the other clinical study enrolled women ≥ 30 years of age).

Case Example: Hepatitis B Virus

The hepatitis B virus 2 PMA involved two pivotal clinical study populations: one targeting the primary study cohort, the other a pediatric cohort. The pediatric clinical study consisted of samples from a population of pediatric patients in Florida at high risk for exposure to viral hepatitis. Demographic characteristics of the pediatric clinical study (n=165) showed that Hispanics represented 42.4% of the study cohort. The higher Hispanic participation in the pediatric study in comparison to the primary study cohort could be explained by the enrollment of patients from a single geographic location where high Hispanic enrollment would be expected. This example illustrates that for studies with few enrollment sites, the demographics of the site may have a substantial effect on the distribution of patients enrolled.

Figure 2-7: Ethnic Composition by Study for Submissions with Two Studies (CDRH)



Abbreviations: N/R = Not reported

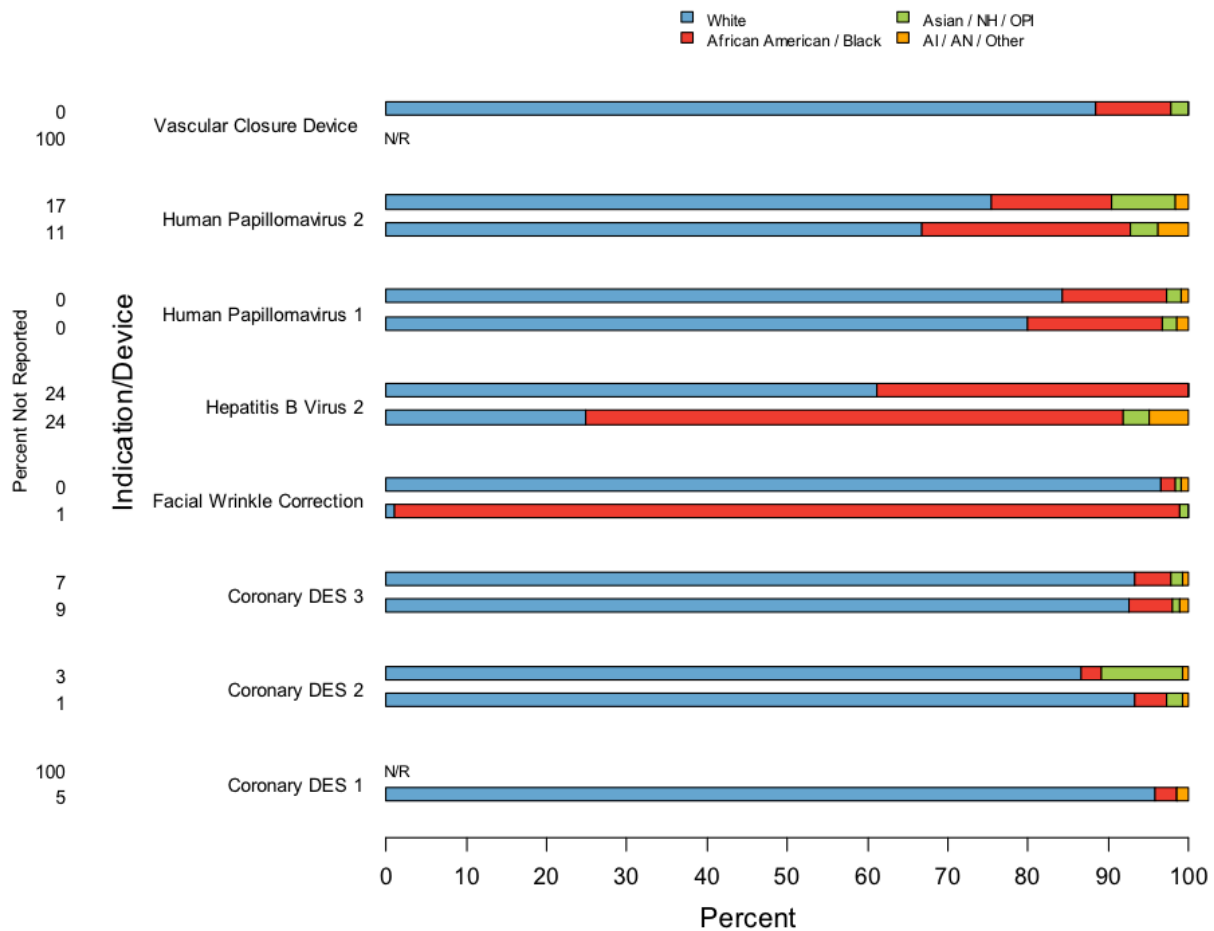
Note: The y-axis for this graph only goes up to 40%.

- Racial Composition

With the exception of the facial wrinkle correction (see Case Example) and the hepatitis B virus 2 PMAs, the racial composition for all of the PMAs with multiple pivotal studies was predominantly White. For two PMAs (vascular closure device and coronary drug eluting stent 1), the racial composition for one of the study cohorts was not reported. Figure 2-8 depicts the racial composition data presented by study for PMAs with two clinical studies.

Case Example: Facial Wrinkle Correction PMA
 The facial wrinkle correction device was evaluated in clinical studies representing the primary study cohort and in patients with Fitzpatrick Skin Phototype Scores \geq IV. The primary study (n=118) enrolled a predominantly White (96.6%) population. Minority populations made up less than 4% of the study population. The sponsor conducted the Fitzpatrick premarket study to better understand the safety and effectiveness of the facial wrinkle correction device in persons of color. The Fitzpatrick clinical study (n=93) enrolled predominantly African American or Black subjects (96.8%).

Figure 2-8: Racial Composition by Study for Submissions with Two Studies (CDRH)



Abbreviations: N/R = Not reported, NH=Native Hawaiian, OPI=Other Pacific Islander, AI=American Indian, AN=Alaska Native

D. Subset Analysis in Applications and Availability of Summary Information

For medical device applications approved in 2011, the working group evaluated the extent to which demographic subset analyses on sex, age, race, and ethnicity were included in PMA applications and summary information was publicly available. Public documents on PMA approvals and evidence of demographic subgroup analyses include the product labeling and the SSED,⁵⁸ which are both posted on FDA's Website, shortly after PMA approval. FDA does not have standard labeling content requirements for devices (apart from the requirements for in vitro diagnostic devices). This results in inconsistent reporting of this information in device labeling. The figures in this section are presented by PMA (n=32 for sex analyses and n=37 for race/ethnicity and age analyses) and include PMAs using the same patient population as another PMA application. Five PMA applications approved for screening for breast cancer or HPV were excluded from the sex analysis because these PMAs enrolled a female-only study population.

Figure 2-9 describes the percentage of PMA applications containing demographic subgroup analyses. Results show that 88% of the PMA applications reviewed contained a sex analysis; 70% contained an age analysis; and 27% contained race or ethnicity analyses. Because only two of the 37 PMAs contained ethnicity subgroup analyses, race and ethnicity were grouped together for this assessment.

Figure 2-10 describes the public availability of summary information (in the device labeling and/or SSED) regarding demographic subset analyses. Results show that 63% of the PMA applications reviewed had a statement conveyed in the device labeling and/or SSED on sex subgroup analysis; 57% had a statement related to an age analysis; and 16% had a statement related to a race or ethnicity analysis. This demonstrates that FDA publicly communicated information on subgroup analyses for sex and age for more than 50% of the PMA applications approved in 2011. Race or ethnicity analyses were submitted in PMA applications and conveyed to the public to a lesser extent.

The findings of the working group highlight that to a large extent demographic subset analyses are present in PMA applications, but FDA's communication to the public of the results of those demographic subset analyses is less consistent.

⁵⁸ An SSED is an FDA document (typically a version is submitted by the applicant and modified by FDA) that is intended to present a reasoned, objective, and balanced critique of the scientific evidence that served as the basis of the decision to approve or deny the PMA. The SSED shows that there was reasonable assurance of safety and effectiveness for the device as labeled based on the nonclinical and clinical studies described in the PMA. The SSED is a summation of both the positive and negative aspects of the PMA. For more, see <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050289.htm#ssed>. Accessed May 25, 2013.

Figure 2-9: Presence of Subgroup Analysis in Applications (CDRH)

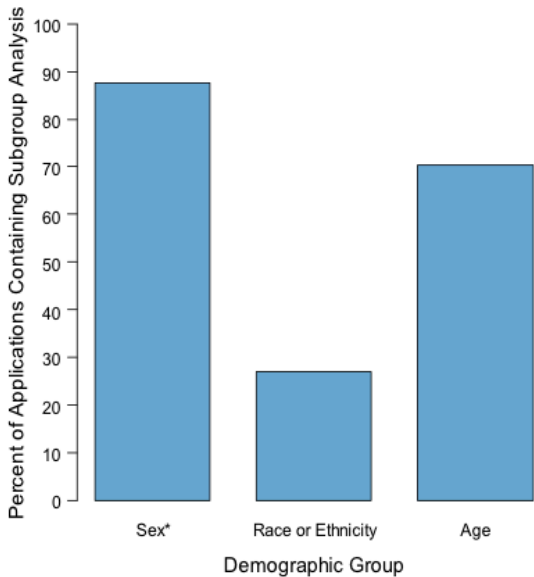
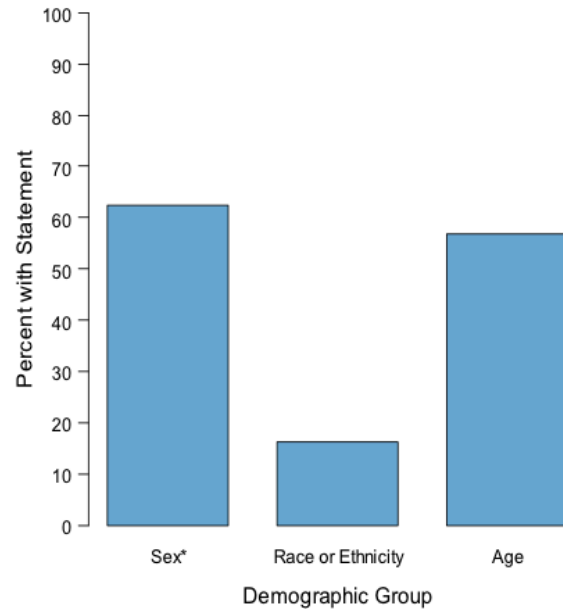


Figure 2-10: Presence of Public Statement about Subgroup Analysis (CDRH)

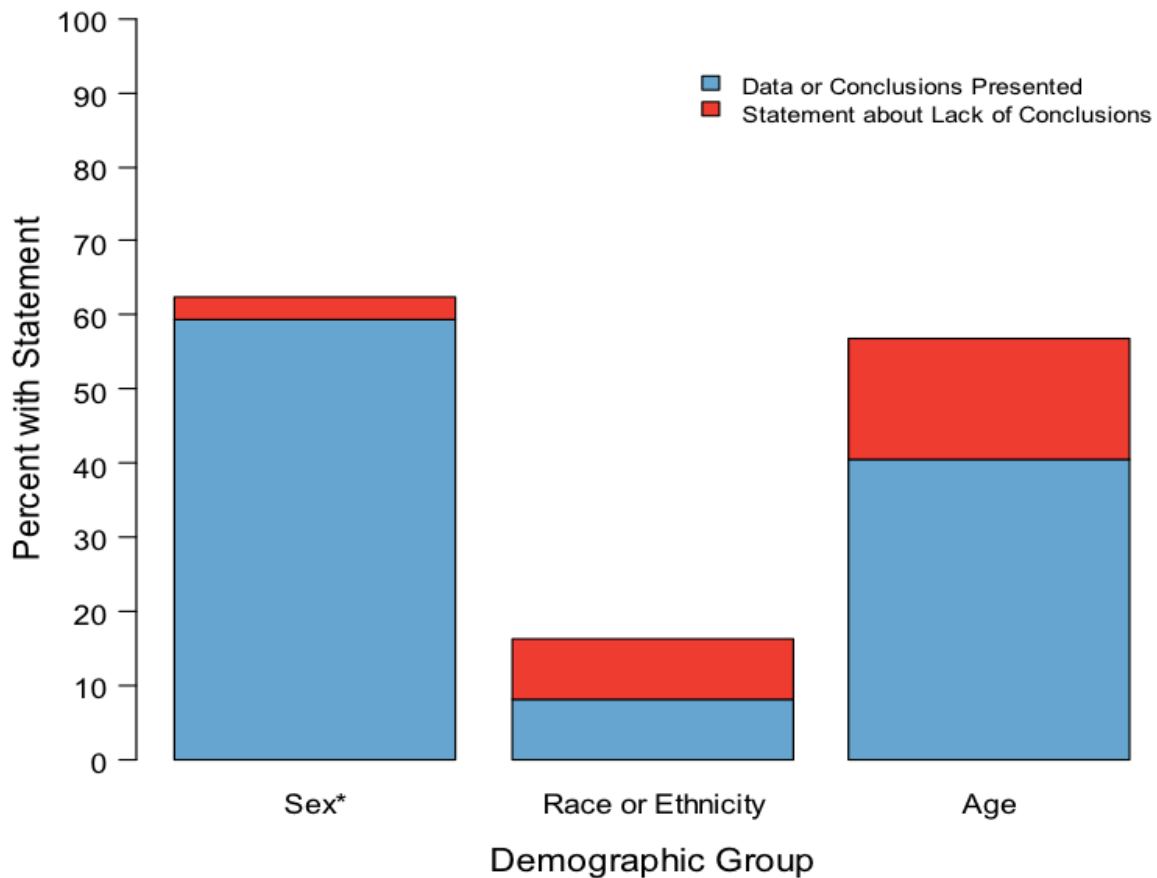


* Excludes five applications with breast cancer or human papillomavirus indications

Figure 2-11 describes the percentage of PMA applications that publicly convey (in device labeling and/or SSED) summary information on demographic subset analyses, indicated by whether data or conclusions were presented or whether only a statement was included regarding lack of conclusions from subset analyses.

For sex and age subset analyses, there was a higher proportion of PMAs that presented data or conclusions compared to PMAs that included only a statement about lack of conclusions regarding demographic subset analyses. For race or ethnicity subset analyses, the same proportion of PMAs had data or conclusions or a statement about lack of conclusions regarding subset analyses.

Figure 2-11: Presence of Public Statement about Subgroup Analysis (CDRH)



* Excludes five applications with breast cancer or human papillomavirus indications

E. Summary of Findings for Part 2: Medical Devices

In summary, the general findings based on this 2011 sampling of medical devices and diagnostics reviewed for this report include the following:

- All PMA applications reported trial composition by sex and age, and the majority of the submissions reported race and ethnicity composition. Demographic subset analyses were more commonly available for sex and age than for race or ethnicity.
- FDA considered demographic subset analyses in PMA applications more often than was presented in device labeling and FDA communications. Moreover, nearly one quarter of

the PMAs contained a second pivotal study cohort, which was designed to obtain clinical experience in a specific subpopulation.⁵⁹

- The representation of demographic subgroups varied widely by product area. This is because a number of factors can influence the interpretation and clinical relevance of demographic information (e.g., intended population for use, prevalence of disease, study sample size).
- Although it is important to include diverse populations in clinical trials when possible and appropriate, the unique nature of medical devices means this additional information would not always be contributory to FDA's decision making. For example, certain microbiology in-vitro diagnostic devices (IVDDs) have high overall accuracy; when this occurs, additional analyses by subpopulations would not affect clearance or approval.

FDA Tools for Communicating Demographic Information

When drugs, biologics, and devices are approved for marketing in the United States, FDA approved labeling is made publicly available. Thus, all FDA-approved products have public information about safety and effectiveness available at the time of marketing. As required under Section 916 of the Food and Drug Administration Amendments Act of 2007 (FDAAA),⁶⁰ FDA communicates information about known differences in safety and effectiveness of drugs and biologics by demographic subgroup to the public through a variety of product approval-related documents posted on its Web site. For example, for drugs and biologics, clinical and statistical reviews and product labeling, in addition to other review-related documents, are typically posted on FDA's Web site. Action packages (a comprehensive collection of FDA staff reviews, labeling, selected correspondence, and other relevant documents for an application) for drugs and biologics are required to be posted to FDA's Web site within 30 calendar days of approval for new products or within 30 calendar days of the third Freedom of Information Act (FOIA)⁶¹ request for the action package.⁶² A summary review (summary basis of regulatory action

⁵⁹ Three PMAs evaluated diagnostic devices in specific age subpopulations; one PMA evaluated an aesthetic device to a specific race subpopulation; and four PMAs evaluated cardiovascular devices specifically in patients with smaller blood vessel sizes.

⁶⁰ Food and Drug Administration Amendments Act of 2007. Public Law No.110-85 (September 27, 2007). Available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsToTheFDCA/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm>. Accessed April 4, 2013.

⁶¹ Freedom of Information Act (FOIA). Public Law No 89-487 (July 4, 1966). Available at <http://www.foia.gov/>. Accessed April 4, 2013.

⁶² Standard Operating Policies and Procedures (SOPP) 8401.7 Action Package for Posting. Available at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm211616.htm>. Accessed June 13, 2013.

(SBRA) is required to be posted within 48 hours of approval unless redaction is required.⁶³ For devices, the SSED along with the approval order, device labeling, and other consumer information (e.g., brief overview of the product) are made publicly available. These materials are posted on the Web site shortly after product approval.⁶⁴

A number of FDA-wide posting and disclosure policies apply as well. These policies are set based on legal mandates and technical requirements that must be followed to successfully comply with FDAAA, the Americans with Disabilities Act of 1990 (ADA)⁶⁵ for accessibility under Section 508 of the Rehabilitation Act of 1973,⁶⁶ and other federal statutory requirements.

Tools Related to Pediatric Demographics

FDAAA requires that FDA track and make publicly available certain pediatric information from pediatric clinical trials for all medical products.⁶⁷ Additionally, under PREA, pediatric-focused reviews and labeling changes are posted on a dedicated page on FDA's Web site.⁶⁸ In accordance with FDAAA, FDA's Web site provides information from pediatric studies conducted in response to Written Requests (per Section 505A of BPCA) and pediatric assessments (per PREA). Unless otherwise noted, these reports contain information from both CBER and CDER. On February 19, 2013, FDA issued a proposed rule that requires manufactures to submit publicly available information on pediatric patients (21 years or younger) that suffer from the disease or condition that the devices submitted for FDA approval are intended to treat, diagnose, or cure. This information will help key stakeholders, device manufacturers, and the FDA track what devices are available to pediatric patients and identify unmet pediatric device needs.

Communication of Clinically Significant Findings in Demographic Subgroups

In general, for all medical products, if a review demonstrates that a clinically significant difference, or a notable lack of information, exists in safety or efficacy data for a demographic subgroup, the appropriate document (e.g., clinical review, labeling) will reflect those findings. If

⁶³ Ibid.

⁶⁴ See CDRH Web site. Available at: <http://www.fda.gov/MedicalDevices/default.htm>. Accessed May 9, 2013.

⁶⁵ Americans with Disabilities Act of 1990. Public Law 110-325 (January 1, 2009). Available at <http://www.ada.gov/pubs/adastatute08.pdf>. Accessed March 7, 2013.

⁶⁶ The Rehabilitation Act Amendments of 1973. Public Law No 93-112 (September 26, 1973). Available at <http://www.access-board.gov/enforcement/rehab-act-text/intro.htm>. Accessed March 7, 2013.

⁶⁷ Food and Drug Administration Amendments Act of 2007. Public Law No.110-85 (September 27, 2007). Available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentsToTheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm>. Accessed April 4, 2013.

⁶⁸ See for example, FDA—Biologics PREA Reviews and Labeling Changes. Available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122938.htm>. Accessed April 4, 2013.

significant safety concerns exist for certain subpopulations, this information is provided in the appropriate section of the product labeling (e.g., Warning & Precautions, Pediatric Use, Geriatric Use). Products labeled for pediatric use, are also posted according to the Pediatric Tracking Requirements under FDAAA.⁶⁹

Upon approval of a new drug or biologic for marketing, FDA posts the following documents (as applicable) on the relevant Web site⁷⁰ (i.e., the Action Package):

- Labeling information
- Approval history
- Certain letters (to the company)
- Reviews and related documents (including action packages)
- Risk evaluation and mitigation strategy (REMS)
- Medication guides
- Other important information from FDA

The timeliness with which approved medical product information is posted depends on whether the documents must undergo pre-posting redaction according to the regulations pertinent to confidential information. In general, letters and review packages do require redaction, but labels do not. When redaction is needed, the posting schedule for approval letters and labeling is typically one-to-two days after approval (the approval letter is where information about any postmarket commitments and requirements for the drug or biologic can be found). Action packages take longer to process because of their size and complexity and the amount of time needed prior to posting can range from one week to six months.

For devices, the SSED along with the approval order, device labeling, and other consumer information (e.g., brief overview of the product) are made publicly available. These materials are posted on the Web site generally within a few days of approval.⁷¹

FDA Advisory Committee Meetings

In addition, many FDA products are routinely brought before FDA Advisory Committees during which a medical product's safety and/or effectiveness is discussed. These discussions may include risk–benefit assessments in special populations and presentations from interested

⁶⁹ For the purposes of this report, pediatric data are reported if the primary indication is for pediatrics. However, in general, consistent with the Pediatric Tracking Requirements under the Food and Drug Administration Amendments Act (FDAAA), pursuant to the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, pediatric demographic data for labeling changes are collected in the Pediatric Study Characteristics Database, which is managed by FDA's Office of Pediatric Therapeutics (OPT). In collaboration with FDA's Centers, OPT collects pediatric study data and posts them to FDA's Web site.

⁷⁰ For medical products approved in CDER, see Drugs@FDA. Available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed May 9, 2013. For products approved in CBER, see Vaccines, Blood & Biologics. Available at www.fda.gov/BiologicsBloodVaccines/default.htm. Accessed April 4, 2013.

stakeholder groups. Advisory Committee meetings are public meetings, and have background packages and other materials, including full meeting transcripts, posted on FDA's Web site.

Communication of Postmarket Safety Concerns

For all FDA-regulated medical products, if safety concerns are identified in the postmarket period (i.e., after products are approved for marketing), FDA will ensure that appropriate information is communicated to health care professionals and the public through a variety of methods, including the Medwatch safety alert system,⁷² press releases and special communications,⁷³ FDA's social media sites⁷⁴ (Facebook and Twitter accounts), and communication tools that FDA can access when necessary through a variety of partnerships with health care professional and public health associations.⁷⁵

Public Workshops

FDA periodically holds workshops and public meetings on demographic subgroup inclusion and analyses; some examples follow.

- In 1995 a workshop titled *Gender Studies in Product Development: Scientific Issues and Approaches*⁷⁶ explored the science involved with assessing gender effects during development of medical products, including drugs, biologics, and medical devices, and identified significant areas for further research and policy development.
- In 2006, an important workshop titled, *Sex Differences and the FDA Critical Path Initiative*⁷⁷ addressed the importance of understanding the biological differences between men and women in the context of developing tools to improve and accelerate the development of drugs, biologics, and devices.

⁷² Safety—MedWatch Safety Alerts for Human Medical products. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm> Accessed April 4, 2013.

⁷³ Drugs—Drug Safety and Availability. Available at <http://www.fda.gov/Drugs/DrugSafety/default.htm>. Accessed April 4, 2013.

⁷⁴ News & Events—Interactive Media. Available at <http://www.fda.gov/NewsEvents/InteractiveMedia/default.htm#Facebook>. Accessed April 4, 2013.

⁷⁵ FDA guidance *Drug Safety Information – FDA's Communication to the Public*.

Note: FDA guidance documents are available at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>.

⁷⁶ Food and Drug Administration Office of Women's Health. 1995. *Gender Studies in Product Development: Scientific Issues and Approaches*. Available at <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134457.htm>. Accessed May 9, 2013.

⁷⁷ See http://www.womenshealthresearch.org/site/DocServer/FDA_Critical_Path.pdf?docID=1401. Accessed May 9, 2013.

- In 2008, CDRH held two public workshops to discuss ways to overcome barriers to understanding the effect of sex differences on clinical outcomes, with a focus on clinical study conduct and statistical analysis: *Exploration of Public Policy Development Regarding the Study and Analysis of Sex Differences in the Clinical Evaluation of Cardiovascular Medical Products*⁷⁸ and *FDA/Advanced Medical Technology Association (AdvaMed) Workshop: Gender Differences in Cardiovascular Devices*.⁷⁹
- In 2011, a conference titled *Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities*⁸⁰ (cosponsored by the Society for Women’s Health Research) focused on novel methods for improving recruitment and retention of women and minorities, community-based approaches to clinical trial design, federal perspectives on guidelines and regulations to improve diversity in government- and industry-funded research.
- In June 2013, CDRH held the *Health of Women Public Workshop*⁸¹ to discuss how to improve the availability, consistency and communication of sex-specific information for the safe and effective use of medical devices in women, address identified gaps and unmet needs through targeted resources and foster the development of innovative strategies, technology and clinical study models.

Scientific Publications

In addition, scientific publications by FDA review scientists can be a source of relevant demographics information for approved drugs, biologics, and medical devices (see selected examples of relevant FDA publications in Appendix 5).

⁷⁸ See <http://www.medicaldevicestoday.com/2008/06/cdrh-explores-r.html>. Accessed May 9, 2013.

⁷⁹ See <http://www.gpo.gov/fdsys/pkg/FR-2008-11-26/html/E8-28169.htm>. Accessed May 9, 2013.

⁸⁰ See <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm273816.htm>. Accessed May 9, 2013.

⁸¹ See <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346073.htm>.

Summary and Conclusions

FDA has a variety of statutory, regulatory, and policy-related tools that provide a framework for guiding medical product sponsors on the collection and subset analysis of demographic data on the participants in their clinical trials. FDA's internal policies and procedures and regulations facilitate the assessment of demographic subgroup information included in marketing applications. Moreover, following medical product approval, FDA communicates available information to the public on the demographic profile of the study participants and on the demographic data subset analyses using a variety of mechanisms (e.g., consumer updates, safety alerts, label changes, etc.). Our analysis for this report determined that, in general, medical product developers/manufacturers and FDA staff are complying with relevant requirements and guidance. Nevertheless, areas for improvement have been noted, and these findings will be used to inform and guide development of the FDASIA Section 907-required Action Plan.

Congress asked us to consider four topic areas in preparing this report. The highlights from our study include the following:

Tools to ensure submission of demographic information

- Although there is some variation by product area, FDA's statutory and regulatory requirements, guidances, policies, and procedures generally inform sponsors about including tabulations of the demographic data of clinical trial participants and demographic subset analyses in their medical product applications (see Appendix 1).
- Similarly, tools (e.g., application review templates and FDA standard operating policies and procedures) guide regulatory review staff in the assessment of marketing applications to ensure that demographic data and subset analyses are included in the information FDA uses in its review and approval processes.

Extent of demographic subset analyses

- The extent to which demographic subset data were analyzed varied across medical product types (drugs, biologics, and devices). Applications for drugs and biologics addressed subset analyses by sex, race, and age — that is, the applications mentioned demographic subsets in some way. The majority of the device applications contained a subset analysis for age and sex, with a lower percentage of applications containing a subset analysis for race or ethnicity. Inclusion did not necessarily mean that the data on patient subgroups was sufficient for meaningful analysis or to detect relevant subgroup effects. In some of the applications reviewed for this report, the results of the subgroup analyses were limited by low sample size.

Extent of demographic subgroup representation in clinical trials

- All biologics, drugs, and the majority of the medical device applications reviewed for this report 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 area. Although it is important to include diverse populations in clinical trials when possible and appropriate, the unique nature of medical devices means this additional information would not always be contributory to FDA's decision making. For example, certain microbiology in-vitro diagnostic devices (IVDDs) have high overall accuracy; when this occurs, additional analyses by subpopulations would not impact clearance or approval.
- Whites represented a high percentage of clinical trial study participants for biologic, drug, and medical device applications. In many cases, other racial subgroups were underrepresented.

Communication of demographic subgroup information to the public

- FDA's internal policies and procedures and regulations facilitate the assessment of demographic subgroup information included in marketing applications. Moreover, following medical product approval, FDA can communicate available information to the public on the demographic profile of the study participants and on the demographic data subset analyses using a variety of mechanisms: initially with product labeling and publicly posted clinical reviews and later, once the product is on the market, with consumer updates, safety alerts, label changes, and other mechanisms, should this be necessary.
- Statutory differences in the regulatory framework for medical devices compared to those applicable to drugs and biologics account for differences in policies and practices across FDA centers with regard to submission and analysis of demographic data and public disclosure of information at the time a product is approved (e.g., timing of information, information release, and public documents).

There are a number of other important issues to consider when interpreting the results in this report. Apparent differences among demographic groups that can affect health-related behaviors and health outcomes can be influenced by two broad categories of factors that often interact and overlap: (1) *extrinsic factors* (e.g., socioeconomic and cultural influences, diet, environment); and (2) *intrinsic biological factors* (e.g., genetics, hormones, metabolism, organ function, body weight).⁸² Inclusion of broad demographic subgroups (such as diverse racial and ethnic groups)

⁸² FDA guidance *Collection of Race and Ethnicity Data in Clinical Trials*. Note: FDA guidance documents are available at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>.

in clinical trials has the potential to directly address the first category. However, achieving diverse demographic subgroup participation in clinical trials remains a challenge after decades of efforts on the part of the broad stakeholder community, including patients and advocates, industry, academia, and public health agencies. These challenges involve a complex interplay of socioeconomic factors, such as practical considerations for participating in clinical trials (e.g., location of study centers).

As we move into the coming decades, FDA’s regulatory mission will increasingly focus on gathering and understanding information related to the second category, intrinsic factors—genetic and biological influences that affect disease and response to medical products (effectiveness and safety). One of FDA’s goals is to make regulatory decisions based on scientific information and to publicly communicate *actionable* information. That is, when clinically meaningful differences are observed for certain subgroups (e.g., an adverse effect seen more commonly with a certain genetic mutation), this information is included in the product labeling or otherwise publicly released. This information is then used to guide health care professionals in prescribing and monitoring products used by their patients.

The science of variability in human response to medical treatments is driven by many factors, which science is continuing to address over time. In many cases, when demographic subgroup data are collected and analyzed, the response to a drug, a biologic, or a device is generally similar across demographic groups. There are exceptions when clinically meaningful differences in response to a medical product have been observed in certain subgroups of the population. In some cases, genetic or other biological factors may drive variability. In other cases, observed differences may be attributable to other intrinsic or extrinsic factors, or interactions between these or other factors.

For these reasons, there are limitations to focusing on demographic analysis without the context of other factors driving variability. Although it is important to include diverse populations in clinical trials whenever possible and appropriate, the broad self-identified demographic categories used today may not relate to the complex genetic and biological factors that are the basis for differences in response to medical products,^{83,84} although they may be useful in generating hypotheses that may drive additional studies or product development in the future. But in many situations, the demographic subset analysis provided by sponsors may not be actionable. For example, vaccines are generally highly effective in all demographic subgroups. In these cases, FDA has not included information for individual demographic groups in public documents.

It is also important to note that evidence related to the safety or effectiveness of a medical product is based not only on the data from clinical trials, but also on data that may come from a variety of sources once a product is available on the market (e.g., postmarket surveillance). When a product goes on the market, a much broader population uses the product, and if new data

⁸³ Rotimi CN, Jorde LB. Ancestry and disease in the age of genomic medicine. *New Engl J Med* 2010;363:1551-8.

⁸⁴ Jaimes N, Londono V, Halpern AC. The term *Hispanic/Latino*. A note of caution. *JAMA Dermatol* 2013;149:274-5.

suggest an actionable difference in certain groups of patients, FDA communicates this information to the public using a variety of methods.

Our increasing understanding of intrinsic biological factors is improving our ability to tailor treatments at the level of the individual (i.e., *personalized medicine*). Numerous FDA initiatives have been launched to advance the promise of personalized medicine.⁸⁵ These initiatives seek to determine what is the correct medical intervention at the correct time for each patient. This targeted approach is becoming the focus of modern medical product development as scientific advancements delineate the specific genetic variables underlying many diseases.

FDA recognizes the importance in its public health mission of effectively communicating clinically meaningful differences that are observed for certain subgroups, including demographic subgroups, to inform decisions by health care practitioners and patients. To that end, FDA has initiated efforts to develop and publicly release an Action Plan for strengthening the availability of such data, as required in FDASIA Section 907. To support that effort and leverage relevant stakeholder expertise, FDA has opened a docket⁸⁶ in connection with the release of this report to solicit input and recommendations from the public.

⁸⁵ Drugs, Genomics. FDA Web site.

<<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm>. Accessed May 2, 2013

⁸⁶ Comments on this report and related issues can be submitted to the Division of Dockets Management. Submit electronic comments on the report to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Include docket number FDA-2013-N-0745 in our submission.

Appendix 1: Tools for Ensuring Demographic Data Analysis

TABLE 1. DESCRIPTION OF STATUTES 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 FDA and National Institutes of Health (NIH) along with representatives of the drug manufacturing industry to 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 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 NDAs and biologics licensing applications (BLAs) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to 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 with regard to pre- and postmarket drug safety, including the authority to require postmarket studies and clinical trials, safety labeling changes, and Risk Evaluation and Mitigation Strategies (REMS).
2007	CBER/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 biologics 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.

TABLE 1. DESCRIPTION OF STATUES AND REGULATIONS BY CENTER			
YEAR	CENTER	FDA REGULATION	DIRECTION
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 ⁸⁷	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/CBER	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/CBER	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/CBER	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 drugs and biologics can be labeled for pediatric use.
1999	CDER/CBER	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/CBER	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/CBER	Guidance for Industry: Content and Format for Geriatric Labeling [18]	Provides industry with information on submitting geriatric labeling of human prescription drugs and biologics.

⁸⁷ All guidance documents are available at: <http://www.fda.gov/regulatoryinformation/guidances/default.htm>

TABLE 2. FDA GUIDANCE DOCUMENTS BY CENTER			
YEAR	CENTER	GUIDANCE ⁸⁷	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 drugs and biologics (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 the 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 ⁸⁷	DIRECTION
2011	CDER/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 CBER staff to process 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, premature infants, 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 including demographic information and time-dependent covariates to be measured on subjects 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 analysis 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]	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: <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 'filing' 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 a NDA/BLA statistical review relevant to demographical 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 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. 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 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>

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Appendix 2: Products Approved in CDER, Indications, and Abbreviations

Note: Table 2-1: CDER Drugs and Biologics (n=30); Indications (n=31)

	Disease Category	Abbreviated Disease Category	Verbatim Indication from Approved Product Labeling
1.	Chronic Obstructive Pulmonary Disease	COPD (1)	Indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Limitations of Use: (Product) is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
2.	Chronic Obstructive Pulmonary Disease	COPD (2)	Indicated for: The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Important limitations: - (Product) is NOT indicated to treat acute deteriorations of chronic obstructive pulmonary disease. - (Product) is NOT indicated for asthma.
3.	Deep vein thrombosis prophylaxis	DVT	Indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.
4.	Hypertension	HTN	Indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (Product) may be used, either alone or in combination with other antihypertensive agents.
5.	Thrombotic events in acute coronary syndrome	TE/ACS	Indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). (Product) has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (Product) has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of (product). Avoid maintenance doses of aspirin above 100 mg daily.

	Disease Category	Abbreviated Disease Category	Verbatim Indication from Approved Product Labeling
6.	Type 2 Diabetes Mellitus	T2DM	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Important limitations of use: <ul style="list-style-type: none"> • Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis • Has not been studied in combination with insulin
7.	Anaplastic Large Cell Lymphoma	ALCL	Indicated for: <ul style="list-style-type: none"> -The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. -The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. <p>These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with (product).</p>
8.	Acute Lymphoblastic Leukemia	ALL	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to <i>E. coli</i> -derived asparaginase.
9.	Hodgkin's Lymphoma	Hodgkin	Indicated for: <ul style="list-style-type: none"> -The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. -The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. <p>These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with (product).</p>
10.	Transfusional iron overload	Iron Overload	Indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival. Limitation of Use Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.
11.	Melanoma	Melanoma (1)	Indicated for the treatment of unresectable or metastatic melanoma.

	Disease Category	Abbreviated Disease Category	Verbatim Indication from Approved Product Labeling
12.	Melanoma	Melanoma (2)	Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF ^{V600E} mutation as detected by an FDA-approved test. Limitation of Use: (Product) is not recommended for use in patients with wild-type BRAF melanoma.
13.	Myelofibrosis	Myelofibrosis	Indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.
14.	Anaplastic lymphoma kinase - positive non-small cell lung cancer	NSCLC	Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with (product).
15.	Prostate cancer	Prostate CA	Indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.
16.	Thyroid cancer	Thyroid CA	Indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of (product) in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of (product).
17.	<i>Clostridium difficile</i> -associated diarrhea	C. Diff	Indicated in adults (≥18 years of age) for treatment of <i>Clostridium difficile</i> -associated diarrhea.
18.	Head lice	Head lice	Indicated for the topical treatment of head lice infestations in patients four (4) years of age and older.
19.	Hepatitis C	Hep C (1)	Indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years of age or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. (Product) must not be used as a monotherapy.

	Disease Category	Abbreviated Disease Category	Verbatim Indication from Approved Product Labeling
20.	Hepatitis C	Hep C (2)	Indicated, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers. - (Product) must not be used as monotherapy and must only be used in combination with peginterferon alfa and ribavirin. - A high proportion of previous null responder (particularly those with cirrhosis) did not achieve Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with (product). - (Product) efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes (product) or other HCV (hepatitis C virus) NS3/4A protease inhibitors.
21.	Human Immunodeficiency Virus	HIV	Indicated: In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients. The following points should be considered when initiating therapy with (product): - More (product) treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy. - The observed virologic failure rate in (product) treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz. - More subjects treated with (product) developed lamivudine/emtricitabine associated resistance compared to efavirenz.
22.	Hereditary angioedema	HAE	Indicated for treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.
23.	Organ rejection	Organ rejection	- Indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. - Use in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Limitations of Use: - Use only in patients who are EBV seropositive. - Use has not been established for the prophylaxis of organ rejection in transplanted organs other than the kidney.

	Disease Category	Abbreviated Disease Category	Verbatim Indication from Approved Product Labeling
24.	Systemic lupus erythematosus	SLE	Indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. Limitations of Use: The efficacy has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Has not been studied in combination with other biologics or intravenous cyclophosphamide. Use is not recommended in these situations.
25.	Seizures (Lennox-Gastaut)	Lennox-Gastaut	Indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.
26.	Major depressive disorder	MDD	Indicated for the treatment of major depressive disorder (MDD). The efficacy of (product) was established in two 8-week, placebo-controlled trials in adult patients with MDD.
27.	Magnetic Resonance Imaging	MRI	Indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.
28.	Restless legs syndrome	RLS	Indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults.
29.	Partial-onset seizures	Seizures	Indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older.
30.	Single photon emission computed tomography imaging for Parkinsonian syndromes	SPECT	A radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, (product) may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). (Product) is an adjunct to other diagnostic evaluations.
31.	Age-related macular degeneration	AMD	Indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

Appendix 3: U.S. Census Bureau 2011 “People Quick Facts”

People Quick Facts	United States
Population, 2011 estimate	311,591,917
Population, 2010 (April 1) estimates base	308,745,538
Population, percent change, April 1, 2010 to July 1, 2011	0.9%
Population, 2010	308,745,538
Persons under 5 years, percent, 2011	6.5%
Persons under 18 years, percent, 2011	23.7%
Persons 65 years and over, percent, 2011	13.3%
Female persons, percent, 2011	50.8%
White persons, percent, 2011 (a)	78.1%
Black persons, percent, 2011 (a)	13.1%
American Indian and Alaska Native persons, percent, 2011 (a)	1.2%
Asian persons, percent, 2011 (a)	5.0%
Native Hawaiian and Other Pacific Islander persons, percent, 2011 (a)	0.2%
Persons reporting two or more races, percent, 2011	2.3%
Persons of Hispanic or Latino Origin, percent, 2011 (b)	16.7%
White persons not Hispanic, percent, 2011	63.4%

United States Census Bureau, State and County QuickFacts. Available at <http://quickfacts.census.gov/qfd/states/00000.html>, 2012. Accessed November 28, 2012.

Appendix 4: Indications for Medical Device PMAs

Note: The table below includes the complete indications for use associated with each premarket approval (PMA) identified in the figures and report. There were 37 PMAs with 33 unique datasets.

	DEVICE TYPE	INDICATION
1.	Pacemaker (Device)	<p>Indicated for use as a system implanted with two leads. A complete system is required for use in the MRI environment. Indicated for the following:</p> <ul style="list-style-type: none"> • Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity. • Accepted patient conditions warranting chronic cardiac pacing include: <ul style="list-style-type: none"> ○ symptomatic paroxysmal or permanent second-degree or third-degree AV block ○ symptomatic bilateral bundle branch block ○ symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders ○ bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias <p>The device is also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:</p> <ul style="list-style-type: none"> • Various degrees of AV block to maintain the atrial contribution to cardiac output • VVI intolerance (for example, pacemaker syndrome) in the presence of persistent sinus rhythm <p>Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrhythmias In bradycardia patients with one or more of the above pacing indications.</p> <p>Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in bradycardia patients with atrial septal lead placement and one or more of the above pacing indications.</p>
2.	Vascular Closure Device	<p>Indicated for femoral artery puncture site closure, reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional catheterization procedures using a standard 5F, 6F, or 7F vascular sheath introducer with up to 12 cm working length. Indicated to reduce times to hemostasis and ambulation in patients who have undergone interventional catheterization procedures, using a standard 6F vascular sheath introducer up to a 12 cm working length, who have received preprocedural and/or intraprocedural glycoprotein (GP) IIb/IIIa inhibitor therapy.</p>
3.	Coronary DES 1 (Device)	<p>Indicated for improving luminal diameter for the treatment of <i>de novo</i> lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length.</p>
4.	Coronary DES 2 (Device)	<p>Indicated for improving luminal diameter in patients with symptomatic heart disease due to <i>de novo</i> lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter <i>in lesions</i> ≤ 28 mm in length.</p>

	DEVICE TYPE	INDICATION
5.	Coronary DES 3 (Device)	Indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to <i>de novo</i> native coronary artery lesions (length ≤ 32 mm) with reference vessel diameters of ≥ 2.25 mm to ≤ 4.25 mm.
6.	Renal Stent 1 (Device)	Indicated for use in patients with atherosclerotic disease of the renal arteries following sub-optimal percutaneous transluminal renal angioplasty (PTRA) of a <i>de novo</i> or restenotic lesion (≤ 18 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 - 7.0 mm. Suboptimal PTRA is defined as $\geq 50\%$ residual stenosis, ≥ 20 mmHg systolic or ≥ 10 mmHg mean translesional pressure gradient, or flow-limiting dissection.
7.	Renal Stent 2 (Device)	Indicated for use in patients with atherosclerotic disease of the renal arteries following sub-optimal percutaneous transluminal renal angioplasty (PTRA) of a <i>de novo</i> or restenotic atherosclerotic lesion (5 - 15 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 - 7.0 mm. Suboptimal PTRA is defined as $\geq 50\%$ residual stenosis, ≥ 20 mmHg peak systolic or ≥ 10 mmHg mean translesional pressure gradient, flow-limiting dissection, or TIMI [Thrombolysis In Myocardial Infarction] flow < 3 .
8.	Prosthetic Aortic Heart Valve 1 (Device)	Indicated as a replacement for a diseased, damaged, or malfunctioning native or prosthetic aortic heart valve.
9.	Prosthetic Aortic Heart Valve 2 (Device)	Indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.
10.	Thoracic Stent Graft (Device)	Intended for the endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta in patients having appropriate anatomy, including: <ul style="list-style-type: none"> • iliac/femoral access vessel morphology that is compatible with vascular access techniques, devices, and/or accessories; • non-aneurysmal aortic diameter in the range of 18-42 mm; and • non-aneurysmal aortic proximal and distal neck lengths ≥ 20 mm.
11.	Non Paroxysmal Atrial Fibrillation (Device)	Intended to ablate cardiac tissue for the treatment of persistent atrial fibrillation (sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion) or longstanding persistent atrial fibrillation (continuous atrial fibrillation of greater than one year duration) in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.
12.	Endovascular Occlusion Device	Indicated for temporary endovascular occlusion of blood vessels below the neck up to 4 mm in diameter.
13.	Iliac Stent (Device)	Indicated for improving iliac luminal diameter in patients with <i>de novo</i> and restenotic lesions in the common and external iliac arteries, with reference vessel diameters between 6 mm and 10 mm and lesion lengths up to 61 mm. The stent is intended as a permanent implant.
14.	Sinus DES (Device)	Intended for use in patients ≥ 18 years of age following ethmoid sinus surgery to maintain patency, thereby reducing the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The Propel™ separates mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces edema.

	DEVICE TYPE	INDICATION
15.	Melanoma 1 (Diagnostic)	<p>Intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. Designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy. Should NOT be used to confirm a clinical diagnosis of melanoma.</p> <p>Device is only for use by physicians trained in the clinical diagnosis and management of skin cancer (i.e., dermatologists) who have also successfully completed a training program in the appropriate use.</p> <p>The device result is one element of the overall clinical assessment. Positive lesions (which may include malignant melanoma, melanoma in situ, high grade dysplastic nevi and atypical melanocytic proliferation/hyperplasia) should be considered for biopsy; the biopsy decision of a negative lesion should be based on the remainder of the entire clinical context. Lesions that are “non-evaluable” by should be carefully re-evaluated for biopsy.</p> <p>Indicated only for use on lesions with a diameter between 2 mm and 22 mm, lesions that are accessible by the imager, lesions that are sufficiently pigmented (i.e. not for use on non-pigmented or skin-colored lesions), lesions that do not contain a scar or fibrosis consistent with previous trauma, lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions), lesions greater than 1 cm away from the eye, lesions which do not contain foreign matter, and lesions not on special anatomic sites (i.e., not for use on acral, palmar, plantar, mucosal, or subungual areas). Device is not designed to detect pigmented non-melanoma skin cancers, so the dermatologist should rely on clinical experience to diagnose such lesions.</p>
16.	Melanoma 2 (Diagnostic)	<p>Intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin fixed, paraffin-embedded human melanoma tissue. Intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib.</p>
17.	Facial Wrinkle Correction (Device)	<p>Indicated for injection into the mid-to-deep dermis for correction of moderate to severe facial wrinkles and folds such as nasolabial folds.</p>
18.	Fecal Incontinence 1 (Device)	<p>Indicated for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments.</p>
19.	Fecal Incontinence 2 (Device)	<p>Indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications).</p>
20.	Breast Cancer 1 (Diagnostic)	<p>Intended for dual-color chromogenic visualization of signals achieved with directly labeled in situ hybridization probes targeting the <i>HER2</i> gene and centromeric region of chromosome 17. The Kit is designed to quantitatively determine <i>HER2</i> gene status in formalin-fixed, paraffin-embedded breast cancer tissue specimens. Red and blue chromogenic signals are generated on the same tissue section for evaluation under bright field microscopy. The CISH procedure is automated using instruments.</p> <p>Indicated as an aid in the assessment of patients for whom Herceptin™ (trastuzumab) treatment is being considered. Results are intended for use as an adjunct to the clinicopathologic information currently used for estimating prognosis in stage II, node-positive breast cancer patients.</p> <p>This kit is for <i>in vitro</i> diagnostic (IVD) use only.</p>

	DEVICE TYPE	INDICATION
21.	Breast Cancer 2 (Diagnostic)	<p>Intended for use in determining HER2 gene status by enumeration of the ratio of the HER2 gene to Chromosome 17. The HER2 and Chromosome 17 probes are detected using two color chromogenic <i>in situ</i> hybridization (ISH) in formalin-fixed, paraffin embedded human breast cancer tissue specimens following staining on automated slide stainers (using NexES software), by light microscopy. Indicated as an aid in the assessment of patients for whom HERCEPTIN® (trastuzumab) treatment is being considered. This product should be interpreted by a qualified reader in conjunction with histological examination, relevant clinical information, and proper controls.</p> <p>This reagent is intended for <i>in vitro</i> diagnostic (IVD) use.</p>
22.	Breast Cancer 3 (Diagnostic)	<p>Indicated to generate digital mammographic images that can be used for screening and diagnosis of breast cancer. Intended for use in the same clinical applications as 2D mammography systems for screening mammograms. Specifically, the system can be used to acquire 2D digital mammograms and 3D mammograms. The screening examination will consist of a 2D image set or a 2D and 3D image set. The system may also be used for additional diagnostic workup of the breast.</p>
23.	Hepatitis B Virus 1 (Diagnostic)	<p>For the qualitative determination of the hepatitis B e antigen (HBeAg) in human serum and plasma (potassium EDTA, lithium or sodium heparin) from individuals who have signs and symptoms of hepatitis or who may be at risk for hepatitis B virus (HBV) infection. This assay, in conjunction with other serological and clinical information, is intended only for the determination of chronic infection with hepatitis B virus.</p> <p>The controls are used for monitoring the performance of the assay on the systems. The performance of the control material has not been established with any other HBeAg assay.</p>
24.	Hepatitis B Virus 2 (Diagnostic)	<p>For the <i>in vitro</i> qualitative detection of antibodies to hepatitis B e antigen (anti-HBe) in human adult and pediatric (2 to 21 years old) serum from individuals who have symptoms of chronic hepatitis and those who have recovered from HBV infection. Further assessment of HBV infection (biochemical, serological and/or nucleic acid testing) is required to define the specific disease state. Test performance has not been established for the monitoring of HBV disease or therapy.</p> <p>For use in the calibration of the immunodiagnostic systems when used with the Anti-HBe test for the <i>in vitro</i> qualitative detection of antibodies to hepatitis B e antigen (anti-HBe).</p> <p>For use in monitoring the performance of the Anti-HBe test when used on the immunodiagnostic systems.</p>
25.	Hepatitis B Virus 3 (Diagnostic)	<p>Indicated for the <i>in vitro</i> qualitative determination of total antibodies to hepatitis B core antigen (anti-HBc) in human serum and plasma (lithium heparin, sodium-citrate, K2-EDTA) in adult patients with the symptoms of hepatitis or who may be at risk for hepatitis B (HBV) infection. The detection of total anti-HBc is indicative of a laboratory diagnosis for HBV infection. Further HBV serological marker testing is required to define the specific disease state. The immunoassay's performance has not been established for the monitoring of HBV disease or therapy. The electrochemiluminescence immunoassay "ECLIA" is intended for use on the immunoassay analyzer. Anti-HBc is used for quality control of the Anti-HBc immunoassay on immunoassay analyzer.</p>

	DEVICE TYPE	INDICATION
26.	Hepatitis C Virus (Diagnostic)	<p><i>In vitro</i> reverse transcription-polymerase chain reaction (RT-PCR) assay for use with the reagents and with instruments for the quantitation of hepatitis C viral (HCV) RNA in human serum or plasma (EDTA) from HCV-infected individuals. Specimens containing HCV genotypes 1 - 6 have been validated for quantitation in the assay.</p> <p>Intended for use as an aid in the management of HCV-infected patients undergoing antiviral therapy. The assay measures HCV RNA levels at baseline and during treatment and can be used to predict sustained and non-sustained virological response to HCV therapy. The results from the RealTime HCV assay must be interpreted within the context of all relevant clinical and laboratory findings.</p> <p>Assay performance characteristics have been established for individuals treated with peginterferon alfa-2a or 2b plus ribavirin. No information is available on the assay's predictive value when other therapies are used. Assay performance for determining the state of HCV infection has not been established.</p> <p>Assay is not for screening blood, plasma, serum or tissue donors for HCV, or to be used as a diagnostic test to confirm the presence of HCV infection.</p> <p>Controls are used to establish run validity of the assay when used for the quantitation of Hepatitis C Virus (HCV) RNA in human serum and plasma (EDTA) from HCV infected individuals.</p> <p>Calibrators are for calibration of the assay when used for the quantitative determination of Hepatitis C Virus (HCV) RNA in human serum and plasma (EDTA) from HCV infected individuals.</p> <p>This kit is to be used in conjunction with HCV as an optional contamination control for customer laboratories that are currently using or have previously used amplification technologies that incorporate uracil into the amplification product.</p>

	DEVICE TYPE	INDICATION
27.	Human Papillomavirus 1 (Diagnostic)	<p>Indicated for the detection of Human Papillomavirus (HPV) in patient specimens. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types HPV 16 and HPV 18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).</p> <p>The test is indicated:</p> <ul style="list-style-type: none"> (a) To screen patients 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results to determine the need for referral to colposcopy. (b) To be used in patients 21 years and older with ASC-US cervical cytology results, to assess the presence or absence of high-risk HPV genotypes 16 and 18. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy. (c) In women 30 years and older, the cobas HPV Test can be used with cervical cytology to adjunctively screen to assess the presence or absence of high risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. (d) In women 30 years and older, the cobas HPV Test can be used to assess the presence or absence of HPV genotypes 16 and 18. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. <p>Cervical specimens that may be tested with the test include the liquid based collection media and collection device.</p>
28.	Human Papillomavirus 2 (Diagnostic)	<p>Indicated for the qualitative detection of E6/E7 viral messenger RNA (mRNA) from 14 high-risk types of human papillomavirus (HPV) in cervical specimens. The high-risk HPV types detected by the assay include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The assay does not discriminate between the 14 high-risk types. The use of the test is indicated:</p> <ul style="list-style-type: none"> 1. To screen patients 21 years and older with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to determine the need for referral to colposcopy. The results of this test are not intended to prevent women from proceeding to colposcopy. 2. In women 30 years and older, the assay can be used with cervical cytology to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.
29.	Intracranial Aneurysms (Device)	<p>Indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments.</p>

	DEVICE TYPE	INDICATION
30.	Glioblastoma Multiforme (Device)	Intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM), following histologically or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.
31.	Osteoarthritis (Device)	Indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics, e.g., acetaminophen.
32.	Hip Prosthesis (Device)	Intended for uncemented fixation and as a primary joint replacement prosthesis in total hip arthroplasty for skeletally mature patients suffering at least moderate pain in the hip joint from non-inflammatory degenerative joint disease (NIDJD) and its composite diagnoses of osteoarthritis (OA) or post-traumatic arthritis. Inserts are only intended for use with femoral and acetabular components having matching outer and inner diameters.
33.	Lung Cancer (Diagnostic)	<p>Indicated to detect rearrangements involving the ALK gene via fluorescence <i>in situ</i> hybridization (FISH) in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying patients eligible for treatment with Xalkorie (crizotinib). This is for prescription use only.</p> <p>Pretreatment & Post Hybridization Wash Buffer Kit is used to prepare paraffin-embedded lung cancer tissue sections fixed on positively charged slides for use in fluorescence <i>in situ</i> hybridization (FISH) with DNA FISH probes.</p> <p>The negative control slides are intended for use as an assay control for appropriate hybridization conditions during routine use of the FISH Probe Kit. The negative control slides should be assayed in conjunction with the user's specimen slides according the package insert for the FISH Probe Kit.</p> <p>The positive control slides are intended for use as an assay control for appropriate hybridization conditions during routine use of FISH Probe Kit. The positive control slides should be assayed in conjunction with the user's specimen slides according the package insert for the FISH Probe Kit.</p>

Appendix 5: Examples of FDA Publications on Related Topics

The following is a sample of some of the FDA-authored publications on topics related to demographic subgroups, collection of data on subgroups, and relevant response to products by subgroup.

1. Scott PE, Campbell G. Interpretation of Subgroup Analyses in Medical Device Clinical Trials. *Drug Inf J*. 1998 Jan-Mar; 32(1): 213-220.
2. Evelyn B, Toigo T, Banks D, et al. Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999. *J Natl Med Assoc*. 2001; 93(Suppl. 12): 18S-24S.
3. Huang SM, Miller M, Toigo T, et al. Evaluation of Drugs in Women: Regulatory Perspective. Section 11, Drug Metabolism/Clinical Pharmacology (Section editor: Schwartz, J.; Legato, M (ed)) Principles of Gender-Specific Medicine. 2004; 848-859.
4. Gallo-Torres H, Brinker A, Avigan M. Alosetron: Ischemic Colitis and Serious Complications Of Constipation. *Am J Gastroenterol*. 2006; 101(5): 1080-3.
5. Obias-Manno D, Scott PE; Kaczmarczyk, J, et al. The Food and Drug Administration Office of Women's Health: Impact of Science on Regulatory Policy. *J Women's Health*. 2007 Jul; 16(6):807-817.
6. Huang SM, Temple R. Is This The Drug Or Dose For You? Impact and Consideration Of Ethnic Factors in Global Drug Development, Regulatory Review, And Clinical Practice. *Clin Pharmacol Ther*. 2008;84 (3):287-94.
7. Yasuda SU, Zhang L, Huang SM. The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies. *Clin Pharmacol Ther*. 2008;84(3):417-23.
8. Mummaneni P, Amur S, Frueh F et al. Genetics and Ethnicity Based Recommendations for Testing Cytochrome P450polymorphic Alleles in Clinical Trials. American Society for Clinical Pharmacology and Therapeutics 2009 Annual Meeting; 2009-03-18, *Clin Pharmacol Ther*. 2009;85(Suppl 1):S78.
9. O'Callaghan KM. Solutions for Disparities for Women with Heart Disease. *J Cardiovasc Transl*. 2009 Dec; 2(4): 518-525.
10. Pinnow E, Sharma P, Parekh A, Gevorkian N, Uhl K. Increasing Participation of Women in Early Phase Clinical Trials Approved by The FDA. *Womens Health Iss*. 2009; 19(2):89-93.
11. Takao CM, Takahashi M, Pravica V, et al. Vitamin K Epoxide Reductase Genotype Alters Warfarin Dose Requirements in Pediatric Patients. American Heart Association Scientific Sessions 2008; 2008-11-08 Circulation 2008 Oct 28; 118(18 Suppl 2):S1056.
12. Wang SJ. Bridging Study Versus Pre-Specified Regions Nested in Global Trials. *Drug Info J*. 2009; 43(1):27-34.

13. Yang Y, Carlin AS, Faustino PJ, et al. Participation of Women in Clinical Trials for New Drugs Approved by the Food and Drug Administration in 2000-2002. *J Womens Health*. 2009; 18: 303-310.
14. Kramer DB, Mallis E, Zuckerman BD, et al. Premarket Clinical Evaluation of Novel Cardiovascular Devices: Quality Analysis of Premarket Clinical Studies Submitted to the Food and Drug Administration 2000-2007. *Am J Ther*. 2010 Jan-Feb; 17(1): 2-7.
15. Malik S, Justice R, Sridhara R, et al. Prime Time for Prospective Randomized Trials of Targeted Therapies with Validated Targets in Lung Cancer: FDA Perspective. *J Thromb Haemost*. 2010; 5(6 Suppl. 3):S235-S236.
16. Pos Z, Thomas J, Selleri S, et al. The Impact of Race on Interferon-Alpha Responsiveness: A Genome-Wide Study. Federation of Clinical Immunology Societies 10th Annual Meeting; 2010-06-24. *Clin Immunol*. 2010;135(Suppl.):S45.
17. Yoon SS, Dillon CF, Carroll M, Illoh K, Osthega Y. Effects of Statins on Serum Inflammatory Markers: The U.S. National Health And Nutrition Examination Survey 1999-2004. *J Atheroscler Thromb*. 2010;17(11):1176-82.
18. Sedrakyan A, Sharon-Lise T, Dabic S, et al. Comparative Assessment of Implantable Hip Devices with Different Bearing Surfaces: Systematic Appraisal of Evidence. *BMJ*. 2011 Nov; Vol 343: 1-12.
19. Sweet MP, Fillinger MF, Morrison, TM, et al. The Influence of Gender and Aortic Aneurysm Size on Eligibility for Endovascular Abdominal Aortic Aneurysm Repair. *J Vasc Surg*. 2011 Oct: 54(4): 931-937.
20. Amur S, Parekh A, Mummaneni P. Sex Differences and Genomics in Autoimmune Diseases. *J Autoimmun*. 2012; 38(2-3): J254-65.
21. Coakley M, Fadiran EO, Parrish LJ, et al. Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials. *J Women's Health*. 2012 Jul; 21(7):713-716.
22. Merenda C. Racial/Ethnic Composition of Study Participants in FDA-Approved Oncology New Molecular Entities, 2006-2008. *J Natl Med Assoc*. 2012; 104(9-10):430-5.
23. Soon G, Min M, Struble KA, et al. Meta-Analysis of Gender Differences in Efficacy Outcomes for HIV-Positive Subjects in Randomized Controlled Clinical Trials of Antiretroviral Therapy (2000-2008). *AIDS Patient Care STDs*. 2012; 26(8):444-53.