U.S. REGULATORY LANDSCAPE: DIVERSITY IN CLINICAL TRIALS

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

U.S. Regulatory Landscape: Diversity in Clinical Trials

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1.0 Executive Summary

Over the past decades, there has been an increasing awareness of the need for more diversity in clinical trials (such as enhancing the inclusion of patients from underrepresented communities), to better reflect the anticipated population intended to be treated by medicines and to adequately inform regulatory decisions. Diversity and inclusion (D&I) have become a focus for regulatory agencies and the pharmaceutical industry and further crystalized during the Covid-19 pandemic and in the wake of racial protest to improve social equity.

Regulatory approvals of medicines are based on a positive benefit – risk assessment with "substantial evidence" of efficacy and an acceptable safety profile. Under **U.S. federal law**, "substantial evidence" is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Historically, representation in clinical trials of patients who are not "White" has been low. This means that evidence used in filing packages supporting regulatory approvals for new medicines may be less than ideal for showing safety and efficacy in "non-White" populations, which can limit the clinical utility of trial data in patient care and decision-making.

Under the **Food and Drug Administration and Safety Innovation Act (FDASIA)** of 2012, the FDA Health Authority (FDA) was required to create an action plan for improving their analyses of subgroup participation in clinical trials in order to better understand safety and effectiveness for these groups. In addition, the **Prescription Drug User Fee Act (PDUFA) V** (FY 2013-2017) required the reporting of inclusion of demographic subgroups in clinical trials and transparency of safety effectiveness data by demographic subgroups including sex, age, race, and ethnicity in the FDA's Drug Trials Snapshot. In 2014, the FDA published an **Action Plan** outlining a series of activities intended to "enhance the collection and availability of demographic subgroup data" in clinical trials divided into three overarching priorities:

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

Later, in 2016, the **Cures Act 1.0** came into effect encouraging efforts to improve research related to the health of sexual and gender minority populations. In 2017, the U.S. Congress passed the **Food and Drug Administration Reauthorization Act (FDARA)**, in which the FDA was tasked with investigating barriers to clinical trial enrollment for traditionally underrepresented populations. And the following year, **PDUFA VI** (FY 2018-2022) mandated FDA to discuss clinical trial design and methods that increase enrollment of diverse patient populations. Since then, the FDA has released an increased number of guidelines with D&I considerations. The forthcoming legislations and regulations may help further structure and standardize different aspects of clinical trials (e.g., data collection).

In the past few years, the pharmaceutical industry has slowly been taking action to improve the diversity of participants enrolled in clinical trials. Additional multi-stakeholder efforts are needed to identify sustainable solutions to incorporate future regulatory guidance into near-term clinical trial and research.

This regulatory landscape resource is designed to help identify key U.S. legislation and FDA policy, regulation and guidance as well as regulatory precedent to consider when working to understand and improve D&I of adult patients in clinical trials, focusing on the inclusion of racial and ethnic minorities.

In order to facilitate the work of the Sponsors and stakeholders (e.g., Investigators, Contract research organizations) across the clinical trial ecosystem, relevant recommendations from the regulatory guidelines have been categorized in four practical domains:

- Design (Trial and Protocol)
- Data (Terminology, Collection, Presentation, and Foreign Clinical Data)
- Site (Selection, Enrollment Practices)
- Participant (Eligibility Criteria)

This resource is meant to complement existing publications (e.g., Fashoyin-Aje 2021), non-governmental professional or trade organizations initiatives and toolkits (e.g., ASCO Clinical Trial Participation Diversity, PhRMA's principles on clinical trial diversity, MRCT Center Diversity Toolkit v1.2). It provides regulatory perspectives on the importance of proactive strategies, scientifically and clinically driven, to enhance meaningful representation of U.S. adult patients from racially and ethnically diverse communities in clinical trials to better characterize the benefit-risk profile of medical products and if approved, generalize trial results in clinical practice.

It should be noted that the information in this resource is presented objectively; no opinions made on the information. This resource is meant to help inform decisions on the regulatory requirements and recommendations to ensure an adequate racially and ethnically representation in clinical trial participants; companies are responsible for ensuring their own compliance with all applicable laws and regulations. Clinical trials should be conducted in accordance with GCP principles (including E6(R2)).

2.0 Scope

This 'Regulatory Landscape Resource' collates effective U.S. legislation and FDA Health Authority policy, regulation, and guidance related to diversity and inclusion of adult patients in clinical trials up until February 2022. While comprehensive, this resource may not contain all potentially relevant regulatory sources.

The scope of this regulatory landscape resource includes:

- Effective U.S. legislation and FDA policy, regulation and guidance concerned with diversity and inclusion of adult patients in clinical trials, focusing on the inclusion of racial and ethnic minorities.
- A review of regulatory precedent.
- Perspective on future regulatory landscape to enhance diversity and inclusion in clinical trials.

The scope of this regulatory assessment *does not* include and *is not* intended to reflect:

- FDA policy, regulation, and guidance related to clinical trials and other variables such as sex, gender, age (including elderly and pediatric subpopulations), socio-economic status, and coexisting conditions.
- Ex-U.S. legislation and Health Authorities policy, regulation, and guidance related to diversity and inclusion in clinical trials.
- Interpretation of regulatory requirements.
- An exhaustive set of trial guidance that may apply to the conduct of a clinical trial.
- Specific decision-making recommendations on how to approach site selection and enrollment of patients.

3.0 Summary Table

This section provides an overview of key legislation and Health Authority regulations and guidance effective in the United States to assist in the inclusion of racially and ethnically representative populations in clinical trials (see Table 1).

Relevant recommendations from these regulatory guidelines are categorized in four domains:

- Design (Trial and Protocol), see Table 2
- Data (Terminology, Collection, Presentation, Foreign Clinical Data), see Table 3
- Site (Selection, Enrollment Practices), see Table 4
- Participant (Eligibility Criteria), see Table 5

Table 1. Overview of key effective U.S. legislation, FDA regulations, guidance, and scientific publication

Effective date	Legislation, regulation, guidance	Type of medicines	Design	Data	Site	Participant
June 1998	E5 - Ethnic Factors in the Acceptability of Foreign Clinical Data	drugs, biologics		X		
September 2006	E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data Questions and Answers	drugs, biologics		X		
July 2012	Food and Drug Administration Safety and Innovation Act (FDASIA)	drugs, biologics, devices		X		
October 2012	Prescription Drug User Fee Act (PDUFA) V	drugs, biologics, devices		X		
November 2013	Design Considerations for Pivotal Clinical Investigations for Medical Devices	biologics, devices			X	X
August 2014	FDA Action plan to enhance the collection and availability of demographic subgroup data	drugs, biologics, devices		X		X
October 2016	Collection of Race and Ethnicity Data in Clinical Trials	drugs, biologics, devices		X		
December 2016	21st Century Cures Act	drugs, biologics, devices	X	X		
August 2017	Prescription Drug User Fee Act (PDUFA) VI	drugs, biologics, devices	X			
August 2017	FDA Reauthorization Act of 2017 (FDARA)	drugs, biologics, devices				X

September 2017	Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies	devices	X	X	X	X
April 2018	Special Protocol Assessment	drugs, biologics	X			
November 2020	Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry	drugs, biologics	X		X	X
June 2021	Premenopausal Women with Breast Cancer: Developing Drugs for Treatment	drugs, biologics				X
October 2021	General considerations for clinical studies ICH E8(R1)*	drugs, biologics	X			X
January 2022	Patient Engagement in the Design and Conduct of Medical Device Clinical Studies	devices	X			

***The FDA guidance "General considerations for clinical studies ICH E8" is currently being updated to reflect changes from the newly released ICH E8 Revision 1 (E8(R1)).**

3.1 Design (Trial and Protocol)

Inclusive trial and protocol design approaches can promote downstream efforts to enroll racial and ethnic minorities. To date, a number of regulations, guidances, and publications have outlined both high-level and detailed considerations to action during trial and protocol design in order to increase research efficacy, promote adequate and acceptable protocols, and, overall, facilitate enrollment of diverse patient populations.

Table 2. Recommendations on Design (Trial and Protocol)

Effective Date	Recommendations from legislation, regulation, guidance
December 2016	**21st Century Cures Act** This legislation mandated the National Institutes of Health (NIH) to encourage efforts to improve research related to the health of sexual and gender minority populations.
August 2017	**Prescription Drug User Fee Act (PDUFA) VI** This legislation mandated discussion on clinical trial design and methods that increase enrollment of diverse patient populations.
September 2017	**Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies** As excerpted, the purpose of this guidance is to outline the FDA's expectations and provide recommendations for the evaluation and reporting of age-, race-, and ethnicity-specific data in medical device clinical studies. The primary intent of these recommendations is to improve the quality, consistency, and transparency of data regarding the performance of medical devices within specific age, racial, and ethnic groups. Proper evaluation and reporting of this data can benefit patients, clinicians, researchers, regulators, and others. Additionally, it is important that clinical trials include diverse populations that reflect the intended use population. In general, to achieve an unbiased estimate of treatment effect in the general population, Sponsors should develop a strategy to enroll diverse populations including representative proportions of relevant age, racial, and ethnic subgroups, which are consistent with the intended use population of the device. This guidance includes recommendations and considerations to assist Sponsors in developing such a strategy. FDA recognizes the practical challenges in achieving the appropriate enrollment of diverse populations. This guidance includes recommendations to overcome barriers to enrollment in order to balance these recommendations with least burdensome principles. There are several decision trees captured as figures guiding through the recommendations for varied demographic subgroup-specific statistical study designs (observation studies, comparative studies and outcome studies, as examples).

April 2018	**Special Protocol Assessment (SPA)** A SPA is a process allowing Sponsors to discuss and align with the FDA on the adequacy and acceptability of a study protocol design (e.g., eligibility criteria, dose selection, endpoints and statistical analysis plan) from a scientific and regulatory perspective in view of a marketing approval. Of note, "an SPA agreement does not guarantee that a marketing application will be filed or approved, even if the trial is conducted in accordance with the protocol", this will be a review issue. As part of this SPA application, Sponsors are invited to discuss the "relevance of the population to be studied to the U.S. population in which the product is intended to be used, taking into account sex and age distribution and ethnic diversity reflective of the U.S. population. If the population in the proposed trial is narrow, any plans to study the product in a broader, more diverse population should be described. If the Sponsor has feasibility information indicating that the trial will recruit the majority of enrollees from outside of the United States, the submission should include an explanation of why the results should be considered applicable to a U.S. population, and/or identify additional planned trials that will provide an adequate understanding of the benefits and risks of the therapy for the U.S. population, considering ethnic, genomic, standard of care, and other factors relevant to the specific therapy."
November 2020	**Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry** This guidance, focused on enhancing the diversity of clinical trial populations, outlines various trial design and methodological approaches that will facilitate enrollment of a broader population, for Sponsor consideration. The example approaches below are excerpted from the guidance: • Early characterization of drug metabolism and clearance • Leveraging an adapted or enriched trial design • Early consideration for a broad pediatric development program Consideration for the alternative design and methodological approaches aim to optimize safety and effectiveness across different populations. Further detail into the recommendations is detailed in this guidance, along with expanded considerations for inclusive trial practices and enrollment criteria as noted in subsequent sections of this resource.
October 2021	**General Considerations for Clinical Studies ICH E8(R1)** This International Council for Harmonisation (ICH) guidance notably focuses on internationally accepted principles and practices as well as on the consideration of quality in the design and conduct of clinical trials that will facilitate acceptance of data and results by regulatory authorities. To enhance the diversity of the clinical trial participants, Sponsors are recommended to seek insights from the clinical investigators and

	potential study subjects on the feasibility (eligibility criteria, scheduled study visits and procedures), general relevance of study endpoints and settings to the targeted patient population, and value of a treatment in the context of ethical issues, culture, region, demographics, and subgroups within a targeted patient population. In addition, Sponsors should consider obtaining pharmacokinetic information in sub-populations such as ethnic subgroups.
January 2022	**Patient Engagement in the Design and Conduct of Medical Device Clinical Studies** This guidance encourages Sponsors to seek for input from diverse patient advisors, including those from racially and ethnically diverse populations, when designing medical device clinical studies. As excerpted, this may help to address common challenges faced in these clinical studies and could result in: • Faster study/research participant recruitment, enrollment, and study completion; • Greater study/research participant commitment and retention, resulting in decreased loss to follow-up; • Greater study/research participant adherence resulting in fewer protocol deviations/violations; • Greater study/research participation by diverse patient populations; • Fewer protocol revisions; • Streamlined data collection resulting in better quality data; and • More relevant data on outcomes that matter to patients

3.2 Data (Terminology, Collection, Presentation, Foreign Clinical Data)

Inadequate subpopulation representativeness and/or data collection in clinical trials conducted in the U.S. and/or abroad can impact the benefit and risk assessment of a medical product or device. From a data perspective, the standardization of the terminology - notably for the race/ethnicity variable-, collection and presentation of the data are key to limit the risk of bias and improve consistency, comparability, and interpretation.

Table 3. Recommendations on Data (Terminology, Collection, Presentation, Foreign Clinical Data)

Effective Date	Recommendations from legislation, regulation, guidance
June 1998	**E5 Ethnic Factors in the Acceptability of Foreign Clinical Data** The purpose of this guidance is to describe how clinical data collected in one region could be used to inform regulatory decisions in another region, taking into account the influence of ethnic factors that could potentially affect response to a drug or biological product in some subpopulations.
September 2006	**E5 Ethnic Factors in the Acceptability of Foreign Clinical Data Questions and Answers** This addendum to E5 "introduces the multi-regional clinical trial study design as one means to evaluate treatment response heterogeneity and extrapolation. Multi-regional clinical trials may present special situations for the collection and self-reporting of race and ethnicity."
July 2012	**Food and Drug Administration Safety and Innovation Act (FDASIA)** Section 907 of the FDASIA mandated the FDA to provide Congress with: • an action plan detailing "recommendations for improving the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling; on the inclusion of such data, or the lack of availability of such data, in labeling; and on improving the public availability of such data to patients, healthcare providers, and researchers" • and to indicate the applicability of these recommendations to the types of medical products
October 2012	**Prescription Drug User Fee Act (PDUFA) V** This legislation required: • Reporting of inclusion of demographic subgroups in clinical trials and data analysis • Transparency of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity through the Drug Trials Snapshot program

August 2014	**FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data** To address the mandate from Section 907 of FDASIA, the FDA developed an action plan including two overarching priorities on data quality and transparency. • Quality: Improve the completeness and quality of demographic subgroup data collection, reporting and analysis. • Transparency: Make demographic subgroup data more available and transparent
December 2016	**21st Century Cures Act** This legislation also mandates the submission of the results of NIH-funded clinical trials that include women and minorities to NIH's clinical trial data bank.
October 2016	**Collection of Race and Ethnicity Data in Clinical Trials** The purpose of this guidance is to improve the completeness and quality of demographic subgroup data for more consistent collection of race and ethnicity in clinical trials. It was developed in support of the FDASIA 907 Action Plan. Terminology: Designations from present guidance are social political constructs consistent with the Office of Management and Budget (OMB) Policy Directive 15 and NIH guidance. Any additional details should be traceable to the 2 minimum designations for ethnicity ("Hispanic or Latino" and "not Hispanic or Latino") and 5 minimum designations for race ("American Indian or Alaska Native", "Asian", "Black or African American", "Native Hawaiian or Other Pacific Islander", "White"). The term "nonwhite" is not acceptable. Collection: a 2-step collection process is recommended, requesting the trial participant to self-report ethnicity then race data. Presentation: • Drugs/biologics: tabulated demographic data based on the Demographic Rule, ICH M4E and designations from present guidance. • Devices: further refer to the guidance on "Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies".
September 2017	**Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies** The purpose of this guidance is to improve the quality, consistency, and transparency of data regarding the performance of medical devices within specific age, racial, and ethnic groups. The specific objectives of this guidance, as excerpted, are to: • encourage the collection and consideration during the study design stage of relevant age, race, ethnicity, and associated covariates (e.g., body size, biomarkers, bone density) for devices for which safety, effectiveness (or, for humanitarian device exemptions (HDEs), probable benefit), or benefit-risk profile is expected to vary across these groups; • outline recommended analyses of study subgroup data, with a framework for considering demographic data when interpreting overall study outcomes; and • specify FDA's expectations for reporting age-, race-, and ethnicity-specific information in summaries and labeling for approved or cleared medical devices. Guidance to support the terminology is included within the document, along with FDA's recommendation that the submission of applications containing clinical study data with ethnic and racial demographic data captured as

	two distinct categories. FDA also supports reasoning behind including age-, race- and ethnicity-specific differences and further reinforcing the importance of inclusion of diverse populations that reflect the intended population, especially when clinically meaningful differences in safety, effectiveness, or benefit-risk profile are expected across these groups.

3.3 Site (Selection, Enrollment Practices)

Diversifying the sites and staff involved in clinical trials is another key parameter to become more inclusive and improve patient representativeness. This creates opportunities for raising awareness and facilitating access to clinical trials.

Table 4. Recommendations on Site (Selection, Enrollment Practices)

Effective Date	Recommendations from legislation, regulation, guidance
November 2013	**Design Considerations for Pivotal Clinical Investigations for Medical Devices** This guidance for medical devices recommends selecting investigational sites facilitating recruitment of subjects that adequately represent the target population and ensuring diversity in terms of investigator or operator experience. "Where applicable, special care should be taken to ensure that the study sites will include subjects who reflect the epidemiological distribution of the disease being treated with regard to variables such as sex, age, race, ethnicity, socio-economic status, and coexisting conditions." • "Similarly, depending on the device, it may be important to consider diversity of sites in terms of investigator or operator experience."
September 2017	**Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies** • This guidance for medical devices also outlines the importance of enrolling "diverse populations throughout the enrolling sites, particularly in studies where surgical or operator skill may be of key importance. If patients enrolled at one site are predominantly of one demographic subgroup, it may be possible to incorrectly attribute differences in device performance or surgical skill to demographic subgroups; this should be considered when planning and analyzing trials."

November 2020	**Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry** Inclusive clinical trial practices, as detailed in this guidance, are excerpted below: • "Developing clinical trial protocols, work to ensure that eligibility criteria serve the goal of having a representative sample of the population for whom the drug has been developed and examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study objectives." • "Sponsors should enroll participants who reflect the characteristics of clinically relevant populations with regard to age, sex, race, and ethnicity and more specifically, inclusion of racial and ethnic minorities in clinical trials and the analysis of clinical trial data by race and ethnicity."

3.4 Patient (Eligibility Criteria)

The guidances below recommend approaches that Sponsors can take to increase enrollment of underrepresented populations in clinical trials, as well as to enroll patient populations that accurately reflect the population intended to be treated by medicines being assessed in clinical trials.

Table 5. Recommendations on Patient (Eligibility Criteria)

Effective Date	Recommendations from legislation, regulation, guidance
November 2013	**Design Considerations for Pivotal Clinical Investigations for Medical Devices** This guidance for medical devices recommends that the target population should reflect the epidemiological distribution of the disease being treated with regard to variables such as sex, age, race, ethnicity, socio-economic status, and coexisting conditions. Applicability to the U.S. population and medical practice should be included in the study design. Background information should be included into the protocol and investigator training materials, discussing (sex- and race-specific) prevalence, diagnosis, treatment, proportions of women and minorities included in past trials for the target indication as well as mitigations plans to potential under-representations, as applicable.
August 2014	**FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data** To address the mandate from Section 907 of FDASIA, the FDA developed an action plan including a priority to identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation.

August 2017	**FDA Reauthorization Act of 2017 (FDARA)** Section 610(a)(3) of the FDA Reauthorization Act of 2017 (FDARA) mandated the FDA to issue guidance on approaches that Sponsors can use "to broaden eligibility criteria for clinical trials and expanded access trials, develop eligibility criteria and increase trial recruitment so research subjects more accurately reflect the patients most likely to receive the drug while establishing safe use and substantial evidence of effectiveness, and applying the foregoing to drugs intended for the treatment of rare diseases or conditions."
September 2017	**Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies** This guidance also provides recommendations and considerations • to develop a strategy to enroll diverse populations including representative proportions of relevant age, racial, and ethnic subgroups, which are consistent with the intended use population of the device. • to overcome barriers to enrollment In addition, it provides enrollment resources and recommendations to achieve enrollment targets, incorporating the data considerations.
November 2020	**Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry** With a focus on broadening eligibility criteria to increase diversity of enrollment and inclusion by design, this guidance provides actionable considerations to support inclusive trial practices, including but not limited to recruitment and retention. A few considerations excerpted from the guidance are below: • Thorough evaluation of exclusionary concomitant medications or comorbidities • When possible, consider broadening criteria to include medically complex participants • Consider evolution of exclusion criteria as studies advance from Phase II to Phase III
June 2021	**Premenopausal Women with Breast Cancer: Developing Drugs for Treatment** The purpose of this guidance is to provide recommendations for including premenopausal women in breast cancer clinical trials. The Sponsor should notably ensure to "reflect the racial and ethnic diversity of this patient population to support the assessment of short- and long-term effects of these therapies across clinically relevant subgroups of patients."
October 2021	**General Considerations for Clinical Studies ICH E8(R1)** This guidance also recommends recruitment efforts to ensure the study participants reflect the planned population for the study.

4.0 Regulatory Precedent and Trends

Clinical research challenges during the current pandemic have been a wake-up call for both government- and industry-based trial Sponsors. With an overburdened healthcare system, increased focus on clinical research has once again put a spotlight on longstanding drug development issues, in particular, concerns about the lack of diverse representation within clinical trials. In 2021 alone, the FDA has put out two perspective pieces from senior leaders that continue to stress the importance of clinical trial diversity, engaging community clinics for research, and encouraging prospective diversity plans early in development with potential enforcement implications in the future.

In a JAMA Oncology Perspective article "Promoting inclusion of members of racial and ethnic minority groups in cancer drug development", published July 15th 2021, FDA Officials in the Oncology Center of Excellence (OCE) have set forth a series of measures in OCE's comprehensive plan to diversify cancer drug trials and prospectively develop diversity plans to ensure diverse enrollment in trials.

A summary of those elements important in a diversity plan follows:

- Provide an overview of the disease or condition: Summarize, collect, and discuss available epidemiological data of the disease or condition with respect to the overall population and in minority subgroups.
- Assess the drug development strategy: Describe planned studies that include study design elements such as enrollment strategies, geographic location, and relevant clinical pharmacological data.
- Target enrollment of members of racial and ethnic minority groups: Define and provide justification for the planned accrual of diverse patients.
- Identify measures to enroll a diverse population: Describe strategies and metrics to characterize safety and efficacy and to retain patients and meet diverse accrual goals.
- Delineate justification for deferral to post approval: Describe proposed post approval trials that will provide data on racial and ethnic minority patients, and a timeline for studies.

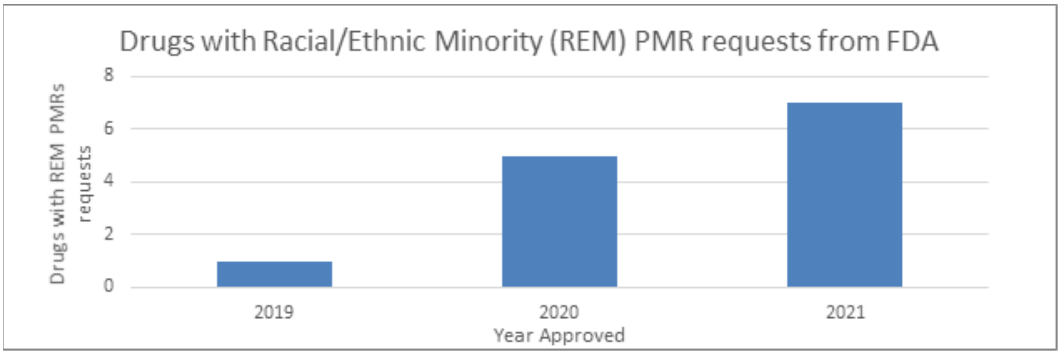
In a NEJM Perspective article "Integrating Research into Community Practice — Toward Increased Diversity in Clinical Trials," published October 7th, 2021. FDA officials explain why now is the time for investments to expand access to clinical research (especially through engaging community clinicians in research), which is an essential component of providing equitable health care to the U.S. diverse populations.

A summary of benefits to integrating community practice into clinical research follows:

- Community practice clinicians have established trusted patient relationships and are committed to addressing the health issues of those populations to allow for transparency and open dialogue.
- Community clinicians have direct insight into unique accessibility challenges faced by diverse patients (e.g., clinicians in the same neighborhoods as their patients might therefore face fewer difficulties with adjustments to work schedules and transportation).
- Enlisting community clinicians could broadly extend the reach of clinical research with their knowledge of what enrollment criteria are achievable and insight into barriers for diverse populations.
- Finally, expanding the pool of clinical researchers will make it easier to translate from research results to clinical care, reduce recruitment delays, and increase the likelihood that the trial population will resemble the products' eventual users.

Furthermore, the FDA launched Project Equity aiming to generate evidence for diverse populations in oncology by ensuring data submitted to the FDA for approval of oncology medical products adequately reflects demographic representation. Recent FDA trends requesting sponsors to consider diverse representation in clinical trials demonstrates an increasingly structured approach to diversity throughout the entire development life-cycle, especially in post-marketing and early clinical development. An independent analysis of FDA's public post-market requirements (PMRs) shows that FDA has increasingly begun to request sponsors to provide additional analyses in the form of either a final report or further trials that include sufficient numbers of racial and ethnic minority (REM) patients to better reflect the U.S. patient population and allow for the interpretation of the results in these patient populations. In 2019 one drug received a REM PMR request, and since then FDA has asked sponsors to conduct REM PMRs within five new drugs in 2020 and within seven new drugs in 2021 (see Table 1 and Figure 1).

Figure 1. Drugs with Racial/Ethnic Minority (REM) Post-Marketing Requirements (PMR) from FDA Since 2019



Source: FDA Postmarket Requirements and Commitments Database

Table 6. Drugs with Racial/Ethnic Minority (REM) Post-Marketing Requirements (PMR) from FDA Since 2019

Year Approved	Therapeutic Area
2019	
BRUKINSA (zanubrutinib)	Oncology
2020	
DARZALEX FASPRO (daratumumab and hyaluronidase-fihj)	Oncology
MONJUVI (tafasitamab-cxix)	Oncology
ORIAHNN (elagolix, estradiol and norethindrone acetate)	Women's Health
SARCLISA (isatuximab-irfc)	Oncology
TAZVERIK (tazemetostat)	Oncology
2021	
EXKIVITY (mobocertinib)	Oncology
LONCASTUXIMAB TESIRINE	Oncology
LUMAKRAS (sotorasib)	Oncology
PEPAXTO (melphalan flufenamide)	Oncology
REZUROCK (Belumosudil)	Oncology
TRUSELTIQ (Infigratinib)	Oncology
UKONIQ (umbralisib)	Oncology
Total	**13**

Source: FDA Postmarket Requirements and Commitments Database

Given the attention the OCE has paid to diversity in clinical trials, it is not surprising to see that the large majority of these recent PMR requests come from the Oncology space, with the exception of the Oriahnn REM PMR within Women's Health. These requests can be very specific, for instance, the PMR for kinase inhibitor, Truseltiq (Infigratinib) for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion, specifically required additional trials to "ensure racial and ethnic minority subjects are adequately represented in the trial population, at a minimum, proportional to the prevalence of FGFR2 alterations in these subgroups in the U.S. population."

In addition to these PMR requests, the FDA has also started to request that Sponsors develop a diversity plan outlining the strategy to collect data to elucidate the impact of race and ethnicity on patient outcomes in early clinical development. At the time of writing this resource, a new FDA guidance document, "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials," was submitted for review at the Office of Management and Budget (OMB) on Jan 18th 2022. Based on the title, this forthcoming guidance is anticipated to further elaborate on a point made in the 2020 Final Guidance "Enhancing the Diversity of Clinical Trial Populations," where FDA stopped short of recommending that sponsors specifically develop proactive plans for ensuring that trial populations are racially diverse, maintaining that the agency only recommends that "sponsors include a plan for inclusion of clinically relevant populations no later than the end of the Phase 2 meeting."

Another possible focus for the forthcoming guidance may be related to defining what constitutes a "health disparity" and how the FDA would interpret "adequate representation" of ethnic and racial minorities in clinical trials. The Agency has previously hinted at borrowing ideas from legislative options, including a little-known provision in Section 18 of the Best Pharmaceuticals for Children Act of 2002, which contains statutory language that would call for diverse enrollment: "In reaching an agreement regarding written protocols, the Secretary [of HHS] shall take into account adequate representation of children of ethnic and racial minorities."

While the focus of the current provision is narrow – only applicable to specific trials that may lead to a six-month marketing exclusivity for pediatric drugs – potential broadening enforcement of the law would have new implications for drug Sponsors to meet "adequate representation" of ethnic and racial minorities in clinical trial protocols. For example, the FDA could decide to withhold exclusivity from a company if it deems a trial design and accrual plan to have resulted in inadequate representation.

Finally, it is worth noting the additional complexities with diverse representation in an increasingly global drug development era. A recent FDA Oncologic Drug Advisory Committee (ODAC) on February 10th 2022 highlighted the challenges FDA had in dealing with trial data exclusively from one country (in this case China) when deciding whether to approve the drug sintilimab for the treatment of patients with Stage IIIB, IIIC, or Stage IV non-squamous NSCLC. Ultimately, the ODAC members voted 14-1 that the FDA should require additional clinical trial(s) demonstrating applicability to U.S. patients and U.S. medical care prior to a final regulatory decision on the application, citing amongst their main reasons for

rejection the lack of clinical trial diversity in the pivotal trial where patients enrolled were younger, more male, and all Asian. The meeting was not a typical ODAC review as FDA Division of Oncology 2 Director Dr. Harpreet Singh noted that "today's ODAC will not follow the traditional paradigm of assessing the benefit-risk profile of a single drug," but "rather, the concept of generalizability and applicability of single-country foreign data to a U.S. population," which "is the central issue for which [FDA] referred this application to the committee."

In short, FDA officials are assessing strategies for ensuring greater diversity in clinical trials as well as considering options for enforcement of diversity. With increasing attention to underrepresentation in clinical trials, it is likely that FDA's requests for diversity plans will continue to become more systematic and frequent for both early clinical development and post-market requirements or commitments. Back in 2016, Robert Califf, the then FDA Commissioner, declared that the year would be The Year of Diversity in Clinical Trials. Given that Califf's nomination successfully passed Congress, it will not be surprising to see the FDA take a proactive approach to clinical research reforms with a renewed focus on diversity in clinical trials.

5.0 Future Regulatory Landscape

In parallel with the FDA's efforts, industry, legislators and regulators have also been working to advance clinical trial diversity efforts through the upcoming reauthorization of the Prescription Drug User Fee Act (PDUFA) VII, the second reiteration of the 21st Century Cures Act (Cures 2.0), and the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act.

Under the **PDUFA VII** Commitment Letter, the FDA explains that Digital Health Technology (DHTs) can enable and advance Decentralized Trials, although the Agency does not explicitly discuss trial diversity. The Agency has committed to publish guidance on the use of DHTs in traditional and decentralized clinical trials by the end of fiscal year 2023 first quarter. As noted above, such efforts can support trial diversity efforts by reducing barriers to participation, especially among persons living outside of convenient proximity to major research centers or by persons who may find it difficult to participate in trials for economic or mobility reasons.

The same **PDUFA VII** Commitment Letter also calls for the use of Real-World Evidence (RWE) to support Post-Marketing Requirements. By the end of 2022, the FDA would need to initiate a pilot program, the Advancing RWE Program, to "identify approaches for generating RWE that meet regulatory requirements in support of […] meeting post-approval study requirements." While that provision is not explicitly intended to support diversity efforts, because post marketing requirements (PMRs) or post marketing commitments (PMCs)) are often intended to fill in gaps in understanding not demonstrated during the pivotal studies, the RWE pilot program could, in effect, be used to support trial diversity efforts. This could especially be the case now that the FDA has launched Project Equity in Oncology in August 2021 and ask Sponsors in PMRs to collect diversity-related data (see Section 4.0: Regulatory Precedent and Trends).

Section 203 of the **Cures 2.0** legislation also discusses increasing diversity in clinical trials. The proposed bill directs a variety of federal stakeholders, including the FDA, the Government Accountability Office (GAO), and HHS to update Congress on, and bolster activities around, diversity in clinical trials. Cures 2.0 directs the FDA to submit an updated report to Congress on its efforts to increase representation in clinical trials, as originally required under the FDA Safety and Innovation Act (FDASIA), and to update its FDASIA-mandated action plan on inclusion of underrepresented demographic subgroups. To support future actions, the bill would also direct GAO to develop recommendations on how to decrease barriers to trial participation "by individuals in underrepresented populations," HHS to develop a "public awareness campaign" about participating in trials and establish a task force to recommend improvements to ClinicalTrials.gov.

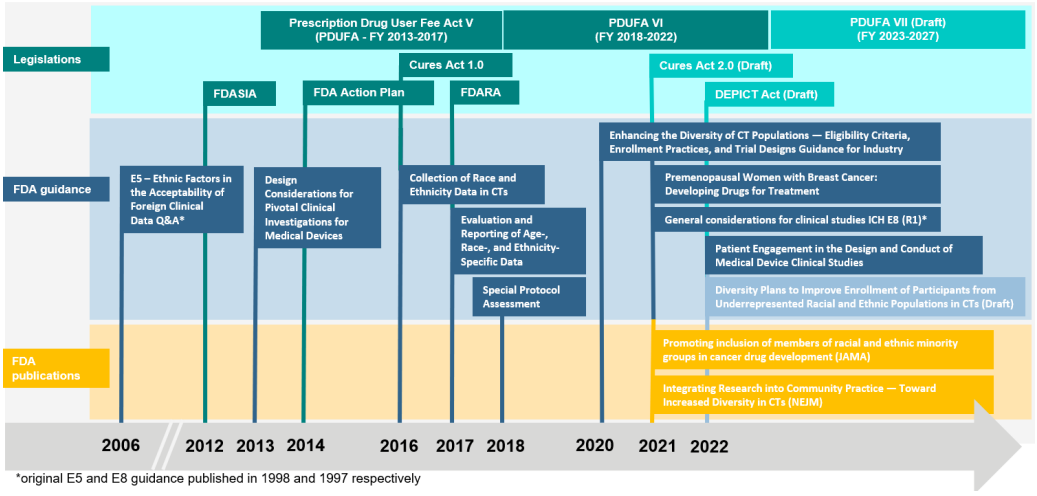
The DEPICT Act's bill was introduced to the House on February 3, 2022 with the aim to strengthen diversity in clinical trials by requiring improved data reporting on clinical trial participant demographics and provide resources to improve access and participation of underrepresented communities in clinical trials. This act includes requirements for Sponsors and FDA. Sponsors would be requested to provide the estimated prevalence in the United States of the disease /condition or a description of the patient population to use the device, clinical trial enrolment targets by demographic subgroup and rationale as well as a Diversity Action Plan detailing how to meet such targets. In addition, Sponsors would be expected to report progress and discuss any challenges in an annual report. The proposed legislation would further require the FDA to publish an annual report on progress to increase diversity in clinical trials. In addition, if enacted into law, this act will provide FDA with the authority to mandate post-marketing studies when sponsors fail to meet clinical trial enrollment targets and do not provide a sufficient justification.

6.0 Conclusion

Since the FDA began work to increase diversity and inclusion efforts in the 1980s, we've seen an Agency evolution that reflects the commitment to and encouragement of greater inclusion and representation of a diverse patient populations in biomedical research leading to the development of medical products. Recent lessons from the COVID-19 vaccine trials suggest that clinical trials can better reflect the diverse demographics of the population when industry publicly commits to representative trials to promote public trust and confidence in the vaccine. For example, certain COVID-19 vaccine trials halted their enrollment for Whites midway through recruitment to allow for more people of color to enroll as companies were forced to get creative in reaching underrepresented and difficult to reach populations through new community partnerships, novel conversations about barriers to trial participation, and identifying processes to ensure community input into research protocols (Andrasik et al., 2021).

Diversity Equity and Inclusion (DE&I) is no longer a "nice to have", but an imperative as seen by the increased inertia in DE&I efforts that continue to shape FDA guidance, perspective pieces published by FDA Officials, and legislative proposals enacted by Congress to address this complex multi-stakeholder issue. Pharmaceutical companies and other stakeholders should be wise to heed the writing on the walls as forthcoming guidance and legislative proposals build upon the lessons of the past decades and push for frequent and systematic inclusion of diverse participation in clinical trials. Increasing diversity in clinical trials is a multi-faceted challenge that will require collaboration from all stakeholders including federal partners, health care professionals, patient advocacy groups, and community-based organizations to ensure lasting and meaningful change.

Figure 2. U.S. regulatory landscape overview on diversity in clinical trials, race and ethnicity focus



7.0 Appendix

7.1 Key Definitions

Biologics (FDA Biological Product Definitions)

Biological products are [...] used to diagnose, prevent, treat, and cure diseases and medical conditions. Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including therapeutic proteins (such as filgrastim), monoclonal antibodies (such as adalimumab), and vaccines (such as those for influenza and tetanus).

Clinical Trial/Study (ICH E6(R2))

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Contract Research Organization (ICH E6(R2))

A person or an organization (commercial, academic, or other) contracted by the Sponsor to perform one or more of a Sponsor's trial-related duties and functions.

Good Clinical Practice (ICH E6(R2))

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Health Authorities / Regulatory Authorities (ICH E6(R2))

Bodies having the power to regulate. In the ICH GCP Guideline, the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Investigator (ICH E6(R2))

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator

Medical Device (FDA FD&C Act)

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals
- intended to affect the structure or any function of the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Participant/Subject/Trial Subject (ICH E6(R2))

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control

Postmarketing commitment (FDA definition)

Postmarketing commitments (PMCs) are studies or clinical trials that a Sponsor has agreed to conduct, but that are not required by a statute or regulation.

Postmarketing requirement (FDA definition)

Postmarketing requirements (PMRs) include studies and clinical trials that Sponsors are required to conduct under one or more statutes or regulations.

Sponsor (ICH E6(R2))

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Study data (ICH E8(R1))

Study data comprises all information generated, collected, or used in the context of the study ranging from existing source data to study-specific assessments. The study data should contain the necessary information to conduct the statistical analysis specified in the protocol and statistical analysis plan, as well as to monitor participant safety, protocol adherence, and data integrity.

Study data can be broadly classified into two types: (1) data generated specifically for the present study (primary data collection) and (2) data obtained from sources external to the present study (secondary data use). Data generated for the study may be collected via case report forms, laboratory measurements,

electronic patient reported outcomes, or mobile health tools. Examples of external sources of data include historical clinical studies, national death databases, disease and drug registries, claims data, and medical and administrative records from routine medical practice. A study may make use of both types of data.

Study protocol (ICH E6(R2))

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Study Site (ICH E6(R2))

The location(s) where trial-related activities are conducted.

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