



PUBLIC MEETING REPORT

Leveraging Real-World Treatment Experience from Expanded Access Protocols

FDA White Oak Campus | Silver Spring, MD | November 19, 2018

About the Reagan-Udall Foundation for the Food and Drug Administration

The Reagan-Udall Foundation for the Food and Drug Administration is an independent 501(c) (3) not-for-profit organization created by Congress to advance regulatory science—science that is critical to helping the U.S. Food and Drug Administration accomplish its mission.

The Foundation works collaboratively with stakeholders including academia, patient groups, industry, and the FDA. The Expanded Access Navigator, an online resource for information and guidance on compassionate use, exemplifies the Foundation’s process of working with public and private stakeholders to develop coordinated resources containing clear information for use by patients, healthcare providers, and others. Industry listings in the Expanded Access Navigator’s directory comply with the 21st Century Cures Act and fulfill the requirement to make expanded access policies “readily available.”

Learn more about the Reagan-Udall Foundation for the FDA at www.reaganudall.org.

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Acronyms and Abbreviations

EA Expanded Access

EAP Expanded Access Programs

EHR Electronic Health Record

FDA U.S. Food and Drug Administration

IND Investigational New Drug

IRB Institutional Review Board

RWD Real-World Data

RWE Real-World Evidence

Organization of the Meeting Report

This Meeting Report summarizes the presentations and discussions that occurred at the *Leveraging Real-World Treatment Experience from Expanded Access Protocols* public meeting held at the FDA White Oak Campus on November 19, 2018. It is not intended to serve as a comprehensive overview of the subject, nor are the citations herein intended to serve as a complete set of references. This report focuses on the issues identified by the speakers and meeting participants

Page five of this report is an Executive Summary for quick reference. Following the report introduction are sections that detail the challenges and the potential strategies for expanded access data collection and use. In the conclusion and next steps, the report presents a call to action based on the proposed strategies from the meeting.

Views expressed in this document are those of the authors and do not necessarily reflect the official policies of the Food and Drug Administration, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Executive Summary

Expanded access, or “compassionate use,” enables patients with serious, life-threatening diseases to access investigational new drugs or therapies outside of clinical trials for treatment.¹ While the primary purpose of expanded access is not evaluative, expanded access does offer a unique opportunity to collect real-world data to generate evidence not gained through clinical trials. Understanding, documenting, and analyzing the experience of expanded access patients has the potential to inform regulatory approval, labeling, reimbursement, research, and most importantly, patient care.

The U.S. Food and Drug Administration has a longstanding history of facilitating and expediting expanded access and currently grants more than 99% of patient requests for investigational therapies.² Expanded access requests may be for a single patient or for more than one patient—in the latter case, with an expanded access protocol.

In working with industry and patient groups, the Reagan-Udall Foundation for the FDA consistently hears about interest in expanded access but also about concerns regarding how data collected through expanded access protocols and single patient access to investigational therapies would be used. As part of the Foundation’s charge to advance science, innovation, and collaboration, the Foundation worked with the FDA to convene nearly 300 patient advocates, physicians, industry representatives, academics, and FDA leaders at the FDA’s White Oak Campus to explore *Leveraging Real-World Treatment Experience from Expanded Access Protocols*, a day-long meeting held on November 19, 2018.

FDA Commissioner Dr. Scott Gottlieb and FDA Principal Deputy Commissioner Dr. Rachel Sherman set the stage for the day’s discussion by providing background on the agency’s history and current focus on real-world evidence. Opening sessions were followed by three expert panel sessions and audience discussion that dove in-depth into stakeholder perspectives, challenges associated with collecting expanded access data, and strategies for improving the collection and utilization of data gathered from expanded access protocols.

Key strategies focus on addressing industry misperceptions about the use of expanded access data in regulatory review, engaging key stakeholders in planning, and improving the quality and consistency of data.

A clear next step needed in leveraging real-world data is creation of a guide on how to run an expanded access data collection pilot. Integrating strategies from the meeting and sharing learnings from current pilot studies will inform best practices that companies could use to standardize expanded access data collection.

¹ U.S. Food & Drug Administration (2018) [21 CFR Sec. 312.300-320 Subpart I-Expanded Access to Investigational Drugs for Treatment Use](#). Accessed on December 12, 2018.

² Jarow, J. P., Lemery, S., Bugin, K., & Lowy, N. (2017). Ten-Year Experience for the Center for Drug Evaluation and Research, Part 2: FDA’s Role in Ensuring Patient Safety. *Therapeutic innovation & regulatory science*, 51(2), 246-249.

Opening Remarks from the FDA Commissioner

Dr. Scott Gottlieb opened the meeting by highlighting U.S. Food & Drug Administration (FDA) initiatives to modernize drug review processes and clinical trials by leveraging digital health tools to generate real-world evidence (RWE).^{3,4} While focused primarily on trial data, the strategies can also be applied to Expanded Access Programs (EAPs) that present an opportunity to generate RWE. The agency looks to overcome previous obstacles to interoperability and data sharing by developing guidance on the use of technology and new statistical tools to help monitor data collection, improve data quality, and inform how studies are conducted. He also emphasized how technologies—from wearables and phone apps to electronic health records—can expand the role of patient-reported outcomes, especially at the point of patient care. Dr. Gottlieb concluded by encouraging a “risk-based approach” to monitoring the most critical data elements and processes involved in clinical trials to ensure data quality and human subject protection.

Introduction

Expanded access (EA), otherwise known as “compassionate use,” is a pathway that grants access to investigational drugs when patients have exhausted all approved treatments and cannot participate in clinical trials.⁵ FDA regulates EA processes to ensure patient protection and that patients and physicians engaged in EA have a clear understanding of a therapy’s risk-benefit profile. The FDA requires reporting of certain data on serious adverse events and a summary report but does not have standard data collection requirements for EA programs, although regulators in some other countries do require data submission.

Drug development and approval is a lengthy process as it entails multiple steps that reinforce patient safety and drug efficacy. The FDA’s role centers on three critical areas in EA: physician qualification, patient informed consent, and safety and efficacy review of other related investigational drugs in the same class. To address critical situations that require patient access to investigational drugs and therapies prior to approval, the FDA has revised its expanded access guidelines. The first EA regulation for emergency single-patient investigational new drug (IND) access was introduced in the 1970s. In later years, the AIDS epidemic demonstrated the need for institutionalizing large-scale EAPs to expand access to

³ U.S. Food and Drug Administration. Framework for FDA’s Real-World Evidence Program. Accessed via <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf> on February, 2019.

⁴ U.S. Food & Drug Administration (2018). Harnessing Real World Evidence for Safety and Innovation. Accessed via <https://www.fda.gov/NewsEvents/Speeches/ucm626164.htm> on December 31, 2018.

⁵ U.S. Food & Drug Administration (2018). [21 CFR Sec. 312.300-320 Subpart I-Expanded Access to Investigational Drugs for Treatment Use](#). Accessed on December 12, 2018.

promising HIV drugs, with FDA developing multi-patient guidance in 1987.⁶ More substantive guidance was released in 2009 with inclusive categorical EA regulations that encompassed single patient requests, intermediate-size groups, and larger treatment EA protocols.⁷

Benefits of Expanded Access Data

While the primary benefit of EA is to provide patients facing serious or life-threatening diseases or conditions an opportunity to receive potential benefits of investigational treatment, it also presents an opportunity to collect RWE that informs payors, industry, regulators, and ultimately, other patients.

The rigor required of clinical trial data for regulatory purposes often limits access to investigational treatment through stringent inclusion/exclusion criteria that define a homogenous population necessary to isolate the effect of the intervention being studied. In contrast, EA programs typically include a broader, more diverse pool of patients, which can expand the applicability of the investigational therapy. These RWD can supplement clinical trial data providing crucial insight from patient and physician-driven experience. Such RWD is especially critical for patients with rare diseases where every dataset is significant due to the small number of patients affected by the disease.⁸

EA data can potentially supplement clinical trial data in the regulatory review of therapies and accelerate drug development in support of safety and efficacy — especially when EA data echo the initial trial findings. Table 1, on page 8, provides examples of how EA data were considered in regulatory approval for a few drugs.

In addition, data collected through EA can inform off-label use and reimbursement if physicians and payors see benefit for a drug outside the indication(s) being studied in the clinical trial, drive label expansion for rare diseases and other patient populations not originally studied, and identify areas of additional research as trends are seen in EA requests, use, and response. Dosing guidelines are another area that can be informed by EA data. For example, EA data informed didanosine (ddI) dosing for patients with advanced HIV that differed from guidelines for patients at an earlier stage of the disease.⁹

⁶ Food and Drug Administration, HHS. (1987). Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations: Treatment Use and Sale. *Fed Regist.* 52:19466–19467.

⁷ Food and Drug Administration, HHS. (2009). Expanded Access to Investigational Drugs for Treatment Use: Final Rule. *Fed Regist.* 74(155):40900–40945.

⁸ U.S. Food & Drug Administration. Accessed via <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf> on February, 2019.

⁹ Pike, IM and Nicalise, C. (1993). The didanosine Expanded Access Program: safety analysis. *Clin Infect Dis. Suppl* 1:S63-8.

Table 1: Examples of Drug Approvals Incorporating EA Data

| Drug Name, Industry Sponsor | Treating Disease | Benefit of EA Data |
|--|--|--|
| Epidiolex <i>(cannabidiol)</i> GW Research Ltd. | Adjunctive treatment of seizures associated with two rare conditions: Lennox-Gastaut syndrome and Dravet syndrome in patients aged 2 and older | Epidiolex approval was supported by an EAP for patients with refractory epilepsy from 38 sites in the US and Australia. The assessment of EAP safety data accounted for almost half of the patients with epilepsy exposed to the drug. Epidiolex was approved June 2018 |
| Lutathera <i>(lutetium lu 177 dotatate injection)</i> Advanced Accelerator Applications | Radio-labeled drug Lutathera for gastroenteropancreatic neuroendocrine tumors. These rare tumors can present in the pancreas and in different parts of the gastrointestinal tract. | EAP in 1,214 patients to support data from a randomized, 229-patient trial. Lutathera injection was approved January 2018 |
| Mepsevii <i>(vestronidase alfa)</i> Ultragenyx Pharmaceutical | Treatment of the rare genetic enzyme deficiency (mucopolysaccharidosis type 7 or MPS VII) disorder that affects fewer than 150 patients worldwide. | Mepsevii safety and efficacy was established from 23 patients (aged from 5 months to 25 years) enrolled in clinical trials and expanded access protocols. Mepsevii was approved November 2017 |
| Voraxaze <i>(glucarpidase)</i> BTG International Inc. | A chemotherapy toxicity reversal agent to treat toxic plasma methotrexate concentrations in patients with impaired renal function. | Clinical evidence for Voraxaze safety was generated from 22 patients in two efficacy studies, including an open-label non-randomized EA protocol. Voraxaze was approved 2012 |

Ethical Considerations of Expanded Access Programs

The ethical debate about EA focuses largely on themes of autonomy, equity, and access — access to treatment, access to research, and even access to knowledge about EA options. Unlike clinical trial data, EA data currently are neither standardized nor routinely provided to the FDA; however, some ethicists argue that, from a moral perspective, data collection should be required any time a drug is tested on a patient so future patients may benefit from the experience.

Patient autonomy and informed consent are at the core, as physicians and patients are often required to make EA treatment decisions based on limited evidence, which is inherently incomplete in early stages of development. Also complicating patient autonomy may be disease severity; some patients may have symptoms that compromise their ability for informed consent.

Equity barriers often fall along socioeconomic lines, including factors such as location and financial burden, which may favor participation from patients with means to travel or cover the cost of treatment. In some communities, physicians and patients may have limited knowledge about clinical trials or EA options and may not have networks in place to ease access.

When use of an investigational therapy is effective, additional access questions may arise: does the company have enough of the drug on hand for all patients in need? What happens to EA patients if the drug does not get approved? What is the drug company's responsibility to a patient who has benefited from the drug but will no longer have access to it? A company's capacity to provide drug access can be limited, especially in the case of gene therapies and other complex biologics where only a limited supply may be available.

Challenges to Expanded Access Data Collection and Use

Expanded access programs are a complex multi-stakeholder engagement requiring collaboration from Institutional Review Boards (IRBs), companies, physicians, academic institutions, and the FDA—each with a vested interest. The meeting explored the challenges faced by each stakeholder in EA data collection. Strategies to address these challenges are presented in the next section of this report.

Provider Capacity for Data Collection

Operational issues and the responsibility of meeting the requirements of investigational therapy protocols may challenge some medical providers and institutions, obligating the treating physician's time and resources often with insufficient reimbursement. Physicians are actively involved in the EA process, as they are required by regulation to determine the risk-benefit of the investigational therapy for their patient based on limited data regarding the safety and/or effectiveness of an investigational agent. Physicians then need to obtain approval from the drug company, IRB, and FDA and are responsible for monitoring and providing certain reports of serious adverse events and, ultimately, a summary report.

Once EA is authorized by the drug company, the physician obtains IRB approval, an independent review to protect the patient and to ensure adequate informed consent. All EA requests require IRB approval, a system in place in most larger medical institutions but not always available in smaller or rural practices. For-profit IRBs, which may save time by expediting IRB approval, can add to the financial burden for the provider. The FDA recently updated the guidelines for single-patient INDs requiring only a single IRB member approval instead of the full IRB membership, which simplifies the review process.¹⁰ Once the treatment is approved by the IRB and FDA, the treating physician then works with the drug company to follow the treatment protocol for the patient(s).

Providers may not have the infrastructure or the financial resources to support data management; thus, collecting and reporting patient data to the drug company and the FDA can tax provider resources and potentially impact data quality. Smaller practices and providers in rural communities may be especially ill-equipped for this demand.

Furthermore, the physician's ability and capacity to monitor the treatment is critical and requires adequate resources and staff for patient management, which can again be particularly challenging for rural physicians or those in low-resource areas.

¹⁰ U.S. Food and Drug Administration (2017) Amended Final Guidance: Expanded Access to Investigational Drugs for Treatment Use –Questions and Answers. Accessed from <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf> on December 31, 2018.

Quality of Data Collected

In addition to the cost and resources involved in EA data collection, quality is also a challenge. In the absence of standardized data collection under Expanded Access Protocols, a retrospective method may be employed, often relying on the electronic health record (EHR) or claims data simply because these are accessible and easily extractable datasets. However, several limitations can compromise the reliability and objectivity of EHR data for regulatory purposes; for example, unstructured data can lead to inconsistencies; there is minimal information specific to the investigational therapy; and important components, such as safety evaluations and outcomes measurements, may be missing. Important quality-of-life measures that explain patient outcomes are not measured in either EHR or claims data.

Industry Concern about Adverse Event Data

Companies developing new drugs may be concerned about the impact of adverse events on the regulatory review and approval of investigational therapies. FDA does not require companies to systematically collect EA data; however, it is expected that sponsors of the IND immediately report to FDA all serious adverse events for which there is evidence to suggest there is a causal relationship between the serious adverse event and the investigational agent.¹¹ The anticipation of potential adverse events may deter some companies from providing EA for fear of a negative impact on their development program, including delays or risks to drug approval, and a higher chance of additional label warnings. This is especially concerning for small companies with their first or only product in the pipeline.

¹¹ U.S. Food and Drug Administration (2018). FDA 21 C.F.R. § 312.305. Accessed on January 23, 2018 via <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.9>

Strategies to Enhance Expanded Access Data Collection and Use

Panelists proposed a number of strategies to optimize expanded access data collection and analysis in the United States, stressing the importance of planning, easing the burden on physicians and patients, and bolstering the quality of data.

Address Industry Misperceptions of EA Data in Regulatory Review

Regulators need to communicate more clearly that EA is an opportunity to enhance a product's regulatory and commercial profile, rather than a risk to its approval and marketing. FDA has issued guidance stating that reviewers recognize that EA treatments occur outside of controlled environments (involvement of confounding factors is considered) and that patients are likely to be at a more advanced stage of the disease, experience comorbidities, and receive other therapies simultaneously.^{12,13} In addition, after reviewing more than 10,000 expanded access protocols from 2005-2015, FDA found that two unexpected deaths temporally associated with investigational drug administration under EA prompted interruption of two clinical development programs but only for a short time.¹⁴ In this same period, the rate of clinical holds for commercial INDs (beyond the initial 30-day safety review) was 7.9%; therefore, the rate of clinical hold due to adverse events on expanded access was 0.2%. Despite the guidance and publication, as noted in the 2018 McKinsey & Co. Report, FDA may need to take additional steps to address industry concerns and misperceptions that EA data harm product development.¹⁵ EA data can, in fact, support expanded labeling and can inform future trial design and regulatory decision-making.

FDA Regulations for EA Data Collection

Panelists cited the need to build a consistent EA data collection process, though across the board, patient advocates, researchers, industry, and regulators agreed that more regulation is not the answer. The FDA's "regulatory flexibility" suits the iterative nature of the drug development and evaluation process, balancing preservation of EA for patients while gathering accurate supplemental RWD. FDA regulation allows an individualized approach

¹² FDA Guidance. Expanded Access to Investigational Drugs for Treatment Use —Questions and Answers Guidance for Industry, Q26. <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>

¹³ Expanded access to investigational drugs for treatment use: final rule. *Fed Regist* 2009;74:40900-40945

¹⁴ Jarow JP, Lemery S, Bugin K, Khozin S, Moscicki R. Expanded Access of Investigational Drugs: the experience of the center of drug evaluation and research over a 10-year period. *Ther Innov Regul Sci*. 2016; 50(6):705–709.

¹⁵ U.S. Food & Drug Administration (2018). Expanded Access Program Report. Accessed on December 31, 2018 from <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm618903.pdf>.

to each development program and helps expedite development of promising therapies, such as breakthrough therapies. Participants recognized that EA programs should not be derailed by requirements for additional data collection. Getting a drug to market is ultimately the best way to provide access and there are several programs available to expedite drug development and therefore decrease the time for drug development and review.¹⁶

Collaborate with FDA in Planning Expanded Access Programs

Engaging the FDA in early stage drug development planning is an often-overlooked step that can make a critical difference in the collection and use of EA data. Connecting with FDA early not only improves understanding of how EA data can be used, but also provides important input on methodology and ensures that approval for single-patient IND requests are not held up by EA plan review.

Involve Patients in EA Planning and Data Collection

Companies should involve patient advocacy groups in designing EA programs long before an EA request is received. Many patients interested in expanded access want to contribute to research, and can help identify quality-of-life indicators. Early consultation will make data more robust and interoperable.

Engaging patients and patient organizations can also help offset ethical concerns by addressing patient knowledge gaps and assisting patients navigating through financial challenges, leading to more comprehensive, inclusive, and informative findings.

Group EA Patients into Cohorts

Providing EA under expanded access protocols—as opposed to single-patient INDs—maximizes the number of patients served and allows for standardization of data collection and reduction of redundancies, thereby reducing operational resources. Early planning to establish a data collection and reporting methodology simplifies the process, which contributes to more consistent, higher-quality data.

Streamline EA Data Points

One approach to strengthen data collection is to reduce data entry burden and collect the most relevant information by focusing on only a few critical data points that can be tracked accurately and consistently. Building a process for consistency of data collection also establishes objectivity. Industry and regulators agreed that a few consistently reported,

¹⁶ U.S. Food & Drug Administration (2018). Harnessing Real World Evidence for Safety and Innovation. Accessed via <https://www.fda.gov/NewsEvents/Speeches/ucm626164.htm> on December 31, 2018.

clinically meaningful data points are of greater value than multiple data points with missing or inconsistent information. Data points should be measurable, objective, definitive endpoints that are easy to collect.

Clarifying the focus of limited data points also allows for better interpretation of collected data. In EA, the loss of randomized controls often leads to the loss of clearly identified causal relationships. Collecting fewer data elements can redirect investment into higher quality data that include repeated measurements for verification, comparison of clinical domain measures, and integration of pathophysiologic impacts. EA data collection is not meant to duplicate a clinical trial, which has separate objectives, a rigorous research protocol, and a heavier financial obligation.

Improve EA Utility of the Electronic Health Record

Since the EHR is a fundamental component of RWD, it can also play a key role in improving what we learn from EA. Introducing five to six fields specific to EA patients in EHRs would help standardize information capture, improve consistency of data, and lessen the data collection burden on physicians. The FDA is involved in an oncology demonstration project with the University of California, San Francisco to examine standard EHR data collection.

Establish EA Patient Registries

Creating a central repository that shares the data and records of EA patients produces an invaluable database for research and comparative study. Patient registries, which could be modeled on the Natural History Study operated by the National Organization for Rare Disorders, would include documentation of disease progression/regression, clinical markers, and treatment responses that could inform drug development and approvals.

Broaden Clinical Trial Criteria

Traditional clinical trials offer rigorous data, yet the challenges posed by stringent criteria generally exclude patients who may be older, sicker, or have comorbid conditions. Companies that worry broadening inclusion criteria may reduce treatment effects could consider enrolling a cohort of patients who do not meet the clinical trial criteria (and may be less likely to see full benefits of the drug) without including the group in the primary endpoint analysis. This way, the company has the benefit of learning from the EA group, but their outcomes would not affect drug efficacy measures. A working group led by the American Society of Clinical Oncology, Friends of Cancer Research, and the FDA collaborated to modify oncology clinical trial inclusion and exclusion criteria while protecting patient safety,¹⁷ which could be replicated for other disease areas.

¹⁷ Jin S, Pazdur R. & Sridhara R. (2017). Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. *J Clin Oncol.* 35(33):3745–3752.

Similarly, patients treated with a specific drug through an EA program may be candidates for a randomized withdrawal study, a type of study discussed at length in FDA's Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.¹⁸ A clear advantage of such an EA study is access to patients with rare conditions who can be recruited almost instantaneously. A randomized withdrawal study should only be considered when the treatment has a reversible symptomatic effect and the drug is not affecting morbidity or survival.

Conclusion

Developing expanded access programs for investigational therapies is an intricate process that relies on harmonized efforts from a multi-stakeholder environment, including industry, patient groups, physicians, IRBs, and the FDA. Expanded access presents an opportunity not only for patients to access potentially life-saving treatment, but also to gather RWD that can improve knowledge and help modernize drug development processes. This daylong meeting and the findings disseminated in this report can inform stakeholders, especially industry and the FDA, in determining how to best leverage real-world treatment experience from expanded access protocols.

Next Steps

A clear next step that emerged from the meeting is the need to pilot and establish best practices for EA data collection. Some of the larger drug companies have already begun EA data pilots, and the FDA is also participating in a few data collection pilots. Integrating strategies from the meeting and sharing process learnings from the pilot studies will inform practices that companies could use to standardize EA data collection without losing the "one-size-doesn't-fit-all" flexibility that companies need to leverage real-world experience from EA protocols.

¹⁸ U.S. Food and Drug Administration (2012), Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. Accessed from <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf> on February 19, 2019.

Acknowledgements

The Reagan-Udall Foundation for the FDA thanks the U.S. Food & Drug Administration for their support in the planning and execution of the public meeting. The Foundation also appreciates the expertise and engagement of the presenters and moderators who donated their time for this event. Please see the meeting agenda included in the Appendix for the full list of presenter names and affiliations.

Appendix A: Meeting Background

The use of an investigational drug outside of clinical trials to treat patients with serious diseases or conditions for which there are no comparable or satisfactory therapies available is commonly referred to as Expanded Access (EA) or Compassionate Use.¹⁹ The Food and Drug Administration (FDA) provides extensive guidance to industry, providers, and patients regarding EA on its website.²⁰ In addition, at the request of FDA and other stakeholder groups, in 2017 the Reagan-Udall Foundation for the FDA launched the Expanded Access Navigator²¹ to assist patients and their physicians in understanding EA and in identifying the potential availability of investigational medicines from companies that provide them via EA programs. The Navigator website provides useful resources and FAQs for patients, physicians, and companies regarding EA, including step-by-step instructions on how to apply for EA.

The Foundation has organized this discussion among various stakeholders, including industry, patient advocacy groups, physicians, bioethicists, and FDA, to explore the potential utility of clinical information gained from EA treatment and possible strategies to collect these data. Today we will hear from experts regarding what real-world data might be generated and how those data might be collected and used to learn from the treatment of patients who receive drugs in EA programs. For these purposes, we define real-world data as observational data generated through clinical treatment and obtained outside of the context of prospective clinical trials.

While clinical trials are the primary source of data, they may have restrictive inclusion and exclusion criteria that limit the use of the trial data to inform the drug label and thus limit the use of the medicine to treat patients. Through EA, patients can receive investigational therapies in a consistent manner that potentially generates reliable real-world clinical information that could supplement results of clinical trials. Data derived from expanded access programs, reflecting real-world treatment experience, could be a source of supplementary information useful in evaluating the drug's safety and efficacy, particularly in cases involving rare diseases and small patient populations.

Data from expanded access treatment may provide additional insights useful in labeling or regulatory decision-making. Biopharmaceutical companies will share their experiences in data collection both in the United States and globally. The regulatory perspective on the usefulness of real-world data in an EA setting will be discussed.

The ultimate goal for companies, physicians and patients is to have a safe and effective drug that is approved by the FDA. Expanded access may have a role in reaching that goal.

¹⁹ For full definition of Expanded Access, see 21 CFR Sec. 312.300-320 Subpart I-Expanded Access to Investigational Drugs for Treatment Use.

²⁰ Expanded Access (2018). Retrieved from U.S. Food & Drug Administration [News & Events]. Accessed on January 15, 2019 from <https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>

²¹ Expanded Access Navigator (2018). Retrieved from Reagan-Udall Foundation for the FDA. Accessed on January 15, 2019 from <http://navigator.reaganudall.org>

Appendix B: Meeting Agenda

- 10:00 am** **Welcome**
Ellen Sigal, Ph.D., Reagan-Udall Foundation Board Chair
- 10:05 am** **Opening Remarks**
Scott Gottlieb, M.D., Commissioner, FDA
- 10:30 am** **Investigational Therapies for Treatment Use: A Historic Perspective**
Rachel Sherman, M.D., Principal Deputy Commissioner Director, FDA
- 10:45 am** **Panel 1: Patient, Physician, and Bioethics Perspectives**
Moderator:
Richard L. Schilsky, M.D., FACP, FSCT, FASCO, Vice-Chair, Board of Directors, Reagan-Udall Foundation, and Senior Vice President & Chief Medical Officer, ASCO
Panelists:
Alison Bateman-House, M.P.H., Ph.D., Assistant Professor, Department of Population Health, New York University School of Medicine
Paul Melmeyer, Director of Federal Policy, National Organization for Rare Disorders
Emil Kakkis, M.D., Ph.D., President/CEO, Ultragenyx
- 12:00 pm** **Lunch Break**
- 12:45 pm** **Panel 2: Industry Case Study Presentations**
Moderator:
Kay Holcombe, Board Secretary, Reagan-Udall Foundation
Panelists:
Paul Aliu, Pharm.D., M.B.A, Global Head, Medical Governance, Novartis
Jayne C. Gershkowitz, Chief Patient Advocate, Amicus Therapeutics
David Meeker, M.D., Chief Executive Officer, KSQ Therapeutics
Joanne Waldstreicher, M.D., Chief Medical Officer, Johnson & Johnson
- 2:15 pm** **Break**
- 2:30 pm** **Panel 3: Expanding Impact of Expanded Access**
Moderator:
Andrew C. von Eschenbach, M.D., President, Samaritan Health Initiatives, Inc.
Panelists:
Jacqueline Corrigan-Curay, M.D., J.D., Director, Office of Medical Policy, CDER, FDA
Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research, FDA
Amy McKee, M.D., Deputy Director, Oncology Center of Excellence, FDA
Peter Stein, M.D., Deputy Director, Office of New Drugs, CDER, FDA
- 4:00 pm** **Public Comments**
- 4:30 pm** **Closing Remarks**
June Wasser, M.A., Executive Director, Reagan-Udall Foundation

Appendix C: Speaker Biographies



Paul Aliu Pharm.D., M.B.A., MRPharmS, G.Dip (Law), PMP

Paul is the Global Head of Medical Governance within the cross-divisional Chief Medical Office at Novartis with responsibility for the oversight, processes, training and systems for compassionate use/expanded access and post-registration medical programs (e.g. Investigator initiated trials, research collaborations, non-interventional studies, registries and Phase IV studies). He has worked in the pharmaceutical industry for over 15 years in multiple roles in drug development, medical affairs and program management covering therapeutic areas such as oncology, rheumatology, transplantation, infectious and tropical diseases. Prior to joining the pharmaceutical industry he trained and practiced as a clinical pharmacist. He previously served as an industry representative on the WHO/Roll-Back Malaria (RBM) case management working group, managed alliances and partnership agreements (Public-Private & Private-Private) with multilateral organizations, NGOs, academic/research institutes; and participated in various round-table and stakeholder discussions on Global Health issues and Patient Access.



Alison Bateman-House, Ph.D., M.P.H., M.A.

Alison is an assistant professor in the Division of Medical Ethics and co-leader of the Working Group on Compassionate Use and Pre-Approval Access. She serves as chair of the Compassionate Use Advisory Committee Infectious Diseases (CompAC ID) and as deputy chair of several other CompACs. She attended the University of Virginia for her BA and Master's of bioethics degrees and Columbia University for her MPH and PhD. She served in the Peace Corps in Cote d'Ivoire; led a team of public health researchers in Louisiana after hurricanes Katrina and Rita; and spent a year "embedded" in the Johns Hopkins Oncology Center, recruiting terminally ill cancer patients for a study investigating these patients' knowledge and understanding of clinical research. She has written and spoken frequently on the history and ethics of using humans as research subjects and on pre-approval access to drugs.



Jacqueline Corrigan-Curay, J.D., M.D.

Jacqueline serves as Director of CDER's Office of Medical Policy (OMP). She leads the development, coordination, and implementation of medical policy programs and strategic initiatives. Dr. Corrigan-Curay brings to the position a unique legal, scientific policy, and clinical background. Before joining FDA, she was at the National Institutes of Health (NIH) in the National Heart, Lung and Blood Institute and the Office of Biotechnology Activities (OBA), Office of Science Policy at NIH. She has held positions as a policy analyst with the Congressional Office of Technology Assessment, and a practicing attorney in Washington, D.C. She practices internal medicine part-time at the Veterans Affairs Medical Center in Washington, D.C.

Dr. Corrigan-Curay earned her law degree from Harvard Law School, her medical degree from University of Maryland School of Medicine, and a bachelor's degree in history of science from Harvard/Radcliffe College.



Jayne Gershkowitz

Jayne joined Amicus Therapeutics in 2006 and serves as Chief Patient Advocate, responsible for developing and executing the global strategies that ensure patients remain at the core of all company operations. A long-time patient advocacy professional, Jayne leads the company's highly regarded Patient & Professional Advocacy department. In addition, Jayne founded the company's Patient Advisory Boards program, has been actively involved in Amicus' public policy work to advocate for policies that satisfy unmet need among those living with rare diseases, and manages *Healing Beyond Disease™*, an Amicus initiative to further serve the rare disease community in extraordinary ways.

Jayne is a 2018 PharmaVOICE 100 honoree, recognized for providing inspiration and innovation in the life sciences industry, and serves on several industry, association and nonprofit boards and committees. She is the former executive director of National Tay-Sachs & Allied Diseases Association. A native of Medford, Massachusetts, Jayne graduated from Syracuse University and studied marketing management at Radcliffe College.



Scott Gottlieb, M.D.

Dr. Scott Gottlieb was sworn in as the 23rd Commissioner of the US Food and Drug Administration on May 10, 2017. Dr. Gottlieb is a physician, medical policy expert, and public health advocate who previously served as the FDA's Deputy Commissioner for Medical and Scientific Affairs and before that, as a senior advisor to the FDA Commissioner.

He also worked as a Senior Adviser to the Administrator of the Centers for Medicare and Medicaid Services, where he supported policy work on quality improvement and the agency's coverage process, particularly as it related to new medical technologies. In 2013 Dr. Gottlieb was appointed by the Senate to serve on the Federal Health Information Technology Policy Committee, which advises the Department of Health and Human Services on healthcare information technology. Dr. Gottlieb was previously a Resident Fellow at the American Enterprise Institute, and a Clinical Assistant Professor at the New York University School of Medicine in Manhattan, where he also practiced medicine as a hospitalist physician.



Kay Holcombe, M.S.

Kay Holcombe is the Secretary, Board of Directors, Reagan-Udall Foundation for the FDA. Before retiring, she was the Senior Vice President for Health Policy at BIO, the Biotechnology Innovation Organization. Prior to this, as Senior Policy Advisor and Vice President for Government Relations at Genzyme, a Sanofi Company, and as Executive Vice President of Policy Directions Inc., a government relations firm. Before joining the private sector, she served as professional health legislative staff and senior health policy advisor in the U.S. House of Representatives and the Senate and senior policy and legislative affairs positions within the FDA, the Health Resources & Services Administration, the National Institutes of Health and, the U.S. Department of Health and Human Services. She received her M.S. in chemistry from the University of Virginia.



Emil Kakkis, M.D., Ph.D.

Dr. Emil Kakkis is currently the Founder and Chief Executive Officer of Ultragenyx Pharmaceutical Inc., a biopharmaceutical company committed to the development of novel therapies for rare and ultra-rare diseases, based in Northern California. In addition, Dr. Kakkis founded and is a current board member of the EveryLife Foundation for Rare Diseases, a non-profit organization dedicated to the acceleration of biotech innovation for rare diseases through practical and scientifically sound improvements to development strategies, regulatory policy and law.

Dr. Kakkis has worked in rare diseases for 27 years as an academic professor, biotechnology and nonprofit foundation leader. Dr. Kakkis is board certified in both Pediatrics and Medical Genetics. He graduated from Pomona College, magna cum laude and received the Vaile prize for his research. He received combined M.D. and Ph.D. degrees from the UCLA Medical Scientist Program and received the Bogen prize for his research.



Peter Marks, M.D., Ph.D.

Dr. Peter Marks is the director of the Center for Biologics Evaluation and Research (CBER) at the FDA. CBER is responsible for assuring the safety and effectiveness of biological products, including vaccines, allergenic products, blood and blood products, and cellular, tissue, and gene therapies.

Dr. Peter Marks received his graduate degree in cell and molecular biology and his medical degree at New York University. Following training at Brigham and Women's Hospital in Boston, he stayed and eventually served as Clinical Director of Hematology. He then moved on to work for several years in industry on the development of hematology and oncology products prior to joining Yale University. He joined the FDA in 2012 as Deputy Center Director for CBER and became Center Director in 2016. Dr. Marks is board certified in internal medicine, hematology and medical oncology, and is a Fellow of the American College of Physicians.



Amy McKee, M.D.

Dr. McKee is the Deputy Director of the Oncology Center of Excellence and the acting Supervisory Associate Director of the Office of Hematology and Oncology Products (OHOP) in the Center for Drug Evaluation and Research of the FDA. Prior to these positions, she was a clinical team leader in OHOP for breast and gynecologic oncology products.

Dr. Amy McKee received her B.A. in Russian and East European Studies from Middlebury College. Before obtaining her medical degree at Tulane University School of Medicine, Dr. McKee was a reporter for Elsevier's medical industry trade journal "The Pink Sheet." She completed her pediatric training at the Floating Hospital for Children/New England Medical Center and her pediatric hematology/oncology training at the combined Johns Hopkins University/National Cancer Institute fellowship program, where she continued basic research on neuroblastoma. She also received the NCI Director's Innovation Career Development Award for her research on stem cells in cancer.

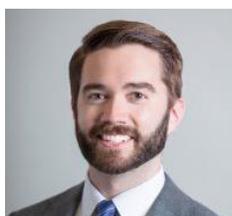


David P. Meeker, M.D.

Dr. Meeker is the President and CEO of KSQ, a biotech company with a proprietary CRISPRomics drug discovery engine. Utilizing this engine, KSQ is advancing a pipeline of oncology and immuno-oncology drug development programs. Dr. Meeker was formerly the President and CEO of Genzyme at the time of its merger with Sanofi in 2011. Within Sanofi, he headed Sanofi-Genzyme, the specialty care unit with responsibility for Rare Diseases, MS, Oncology and Immunology franchises.

Prior to joining Genzyme, Dr. Meeker was at the Cleveland Clinic and Ohio State University. He completed his internal medicine training at Harvard's Beth Israel Hospital and his pulmonary/critical training at Boston University.

Dr. Meeker is the Chairman of the Board of Rhythm Pharmaceuticals, and Trevi Therapeutics and a member of the board at Myokardia. He also serves on the boards of the Biomedical Science Careers Program, the Network for Excellence in Health Innovation and the Dimock Center, a Boston based community health center.



Paul Melmeyer, M.P.P.

Paul Melmeyer M.P.P. serves as the Director of Federal Policy at the National Organization for Rare Disorders (NORD). In this role, Paul engages in federal congressional and regulatory advocacy on behalf of rare disease patients and the organizations that serve them. His overriding mission is to improve the plight of patients with rare diseases and increase incentives for the development of orphan drugs, devices, and diagnostics. Since joining NORD in 2013, Paul has advocated successfully for the passage of various laws and has crafted comments on NORD's behalf for numerous proposed rules and guidances. In 2017, he earned his Master's in Public Policy from the George Washington University. Prior to joining NORD, Paul spent time at the Center for American Progress, AARP, and in the Senate.



Richard L. Schilsky, M.D., FACP, FSCT, FASCO

Richard Schilsky, M.D., FASCO, is the Senior Vice President and Chief Medical Officer of the American Society of Clinical Oncology, Professor emeritus University of Chicago and Vice-Chair, Board of Directors, Reagan-Udall Foundation for the FDA. Dr. Schilsky earned his M.D. at the University Of Chicago Pritzker School Of Medicine. Following a residency at the University of Texas Southwestern Medical Center and Parkland Memorial Hospital, he received oncology training at the National Cancer Institute (NCI).

At the University of Chicago, Dr. Schilsky rose to the rank of Professor of Medicine and served as Director of the University of Chicago Cancer Research Center.

Dr. Schilsky has served on a number of peer review and advisory committees for the NCI and FDA. He has also served as a member of the Board of Directors of the American Society of Clinical Oncology (ASCO) and of the Conquer Cancer Foundation of ASCO and as ASCO President 2008-2009.



Dr. Rachel Sherman, M.D., MPH

Dr. Rachel Sherman is Principal Deputy Commissioner of Food and Drugs at the U.S. Food and Drug Administration (FDA), where she oversees medical programs and initiatives that are cross cutting and clinical, scientific, regulatory, or operational. As the Commissioner's most senior policy advisor, Dr. Sherman provides council on medical product development and regulatory issues and oversees on his behalf high-priority programs and offices, including the Office of Medical Products and Tobacco, Office of Operations, Office of the Chief Scientist, and the Oncology Center of Excellence. Key

areas of current focus include modernizing the agency's organizational structure, streamlining review of combination products, and developing policies around orphan product development, patient engagement, use of real world evidence, prescription drug promotion and patient information, use of innovative trial designs, and standards for evidence development.

She received her MD from Mount Sinai School of Medicine, her MPH from Johns Hopkins University, and her BA in Mathematics from Washington University in St. Louis.



Ellen V. Sigal, Ph.D.

Ellen V. Sigal, PhD, is Chairperson and Founder of Friends of Cancer Research (Friends), a think tank and advocacy organization based in Washington, DC that drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients.

Dr. Sigal is the Chair of the Board of Directors of Reagan-Udall Foundation for the FDA and serves on the Board of the Foundation for the National Institutes of Health, where she chairs its Public Private Partnerships Committee. Additionally, in 2016 Dr. Sigal was named to Vice President Biden's Cancer Moonshot Blue Ribbon Panel, and she holds leadership positions with a broad range of cancer advocacy, public policy organizations and academic health centers including: MD Anderson Cancer Center External Advisory Board, the Duke University Cancer Center Board of Overseers, and The Sidney Kimmel Comprehensive Cancer Center Advisory Council.



Peter Stein, M.D.

Peter Stein is the Deputy Director, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA). He earned his medical degree from University of Pennsylvania and trained at Yale-New Haven Hospital in internal medicine, and in endocrinology and metabolism. He was on faculty at Yale in the Section of Endocrinology and served as the associate program director for the Primary Care Residency Program. Subsequently, Peter was the section chief for endocrinology and the program director for internal medicine residency program at the Medical College of Georgia. Peter has worked at Bristol-Myers Squibb, Merck, Janssen, and returned to Merck as Vice President for late-stage development in Diabetes and Endocrinology. He is a clinical associate professor at the Robert Wood Johnson Medical School, where he maintained a practice in endocrinology for many years. Peter joined FDA in late 2016 as the Deputy Director, Office of New Drugs, CDER.



Andrew C. von Eschenbach, M.D.

Andrew C. von Eschenbach, M.D. entered government service after a career of over three decades as a physician, surgeon, oncologist and executive. He currently serves as President of Samaritan Health Initiatives, Inc., as an Adjunct Professor at University of Texas MD Anderson Cancer Center, as a Senior Fellow at the Milken Institute and previously served as Chair of the Congressional Advisory Panel on 21st Century Cures. He also recently joined the Board of Directors for the Reagan-Udall Foundation for the FDA. He is the 20th Commissioner of the FDA (2005-09). At the FDA, he championed an agenda to modernize the agency. Prior to that he served as the Director of the National Cancer Institute at the National Institutes of Health, where he set an ambitious goal to eliminate the suffering and death due to cancer by rapid acceleration and integration of the discovery-development-delivery continuum.

Dr. von Eschenbach has authored more than 300 scientific papers and has received numerous professional awards and honors. In 2006, he was named one of "The TIME 100: The People Who Shape Our World." Dr.

von Eschenbach earned a B.S. from St. Joseph's University in Philadelphia and his medical degree from Georgetown University.



Joanne Waldstreicher, M.D.

Joanne Waldstreicher, M.D., is Chief Medical Officer, Johnson & Johnson. In this role, she has oversight across pharmaceuticals, devices and consumer products for safety, epidemiology, clinical and regulatory operations transformation, collaborations on ethical science, and technology and R&D policies, including those related to clinical trial transparency and compassionate access. She chairs the R&D development pipeline review committee for Janssen, the pharmaceuticals group of Johnson & Johnson. Joanne is also a Faculty Affiliate of the Division of Medical Ethics, Department of Population Health, New York University School of Medicine.

Joanne received both the Jonas Salk and Belle Zeller scholarships from the City University of New York, and graduated Summa Cum Laude from Brooklyn College. She graduated Cum Laude from Harvard Medical School, completed her internship and residency at Beth Israel Hospital, and her endocrinology fellowship at Massachusetts General Hospital. In 2016, the National Association of Female Executives named her Healthcare Champion of the Year.



June Wasser, M.A.

June S. Wasser, MA joined the Reagan-Udall Foundation for the Food and Drug Administration as Executive Director in May of 2016. In this role, Ms. Wasser provides leadership, oversight and strategic direction for the Foundation's development and implementation of programs and initiatives intended to foster advances in regulatory science in support of the FDA's mission.

Prior to joining the Foundation, Ms. Wasser served as a consultant in translational science programs and the development of continuing medical education programs. Further, Ms. Wasser also has interests in health policy and is a co-editor and co-author on a book about the Affordable Care Act and how policy implementation offers an opportunity for translational research. Ms. Wasser received her MA from the University of California at Los Angeles and completed additional graduate work at the University of Chicago. She served as an Instructor of Medicine at Tufts University.

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