

# Expanded Access Program Report



May 2018

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## Table of Contents

Executive Summary .....	2
Section 1: Background/FDA’s EA Program.....	5
1.1 Background.....	5
1.2 Report Focus—Obtaining Expanded Access.....	6
1.3 Report Organization.....	10
Section 2: Objectives and Methodology .....	11
2.1 Research Objectives.....	11
2.2 Research Methodology .....	11
Section 3: Findings .....	13
Section 4: Recommendations for FDA and Other Stakeholders to Consider.....	22
Section 5: Snapshot of the Stakeholder Roles and the EA Process .....	27
4.1 Stakeholder Roles .....	27
4.2 Process .....	29
Glossary .....	33

## Table of Figures

Figure 1 – High level flow chart for a “typical” single patient EA request.....	9
Figure 2 – EA requests for CDER, CBER and CDRH.....	14
Figure 3 – Turnaround time for CDER and CBER EA requests .....	15
Figure 4 – Turnaround time for CDRH EA requests.....	16
Figure 5 – Mapping of recommendations to the findings they address .....	26
Figure 6 – Patients' view of the EA program stakeholder ecosystem.....	27
Figure 7 – High-level view of the EA process.....	29

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## Executive Summary

Since the 1970s, the U.S. Food and Drug Administration (FDA) has facilitated making investigational drugs available to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. The FDA's Expanded Access (EA) process was formalized through regulation in 1987 (drugs and biologics)<sup>1</sup> and 1996 (devices)<sup>2</sup>, and EA was further codified in law in 1997<sup>3</sup>. The EA program provides a process for patients to obtain authorization to use an investigational medical product for treatment use that has not been FDA approved<sup>4</sup> for use outside of a clinical trial setting.<sup>5</sup> Over the last five years, FDA's Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH) authorized approximately 9,000 applications through the EA program. FDA's EA authorization rate is consistently high—approximately 99% across all application types. As part of FDA's commitment to continuous operational improvement of the EA program, the Agency commissioned an independent assessment of the EA program that considered stakeholder perspectives from across the healthcare ecosystem. The assessment's key goals were to better understand the current EA program's performance and identify ways to improve it.

This report summarizes the results of that independent assessment. The findings reflect the perspectives of patients and their advocates/caregivers, physicians, health system representatives, payers, institutional review boards (IRBs), manufacturers, and FDA staff. Those perspectives were sourced through a variety of quantitative and qualitative methods. The report's principal findings on the overall EA process across the ecosystem are as follows:

- **External stakeholders' overall perceptions of FDA's EA program—and FDA's role, in particular—are positive.** Stakeholders across the healthcare ecosystem highlighted FDA's commitment to expediting the review of EA applications, their collaborative nature, and their focus on continuous improvement. This perception echoed findings in the recent Government Accountability Office (GAO) report<sup>6</sup> as well as numerous sources in the EA literature.
- **Stakeholders report pain points across the physician/patient journey, which, if addressed, could meaningfully enhance the program.** The reported pain points varied significantly based on the respondent's level of experience with the program. Confusion

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<sup>1</sup> Per 21 CFR 312 section I

<sup>2</sup> Per 21 CFR part 812

<sup>3</sup> FDA's EA program is sometimes referred to as the “compassionate use” program. “Expanded access” involves use of an investigational medical product outside of a clinical trial.

<sup>4</sup> “Approved” or “Approval” is used in this report to refer to the following: approval for a drug or device, licensing for a biologic, and marketing authorization for a medical device via the premarket approval, 510(k) or De Novo classification pathway and for a medical device that is exempt from premarket notification to be marketed in the US.

<sup>5</sup> Food and Drug Administration Modernization Act of 1997 (FDAMA).

<sup>6</sup> GAO, *Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used*, July 11, 2017, GAO-17-564, Washington, D.C.: GAO.

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with program navigation, multi-stakeholder coordination, and administrative burden were the most frequently-cited pain points.

- **Because EA operates in an inherently multi-stakeholder environment, the absence of standard processes and policies for EA submission requests to FDA, manufacturers, IRBs, and payers creates confusion for many stakeholders.** Stakeholders reported variability in policies related to requirements for applications submitted to the various parties involved in approval and authorization, in addition to variation in insurance coverage policies. The variation drives administrative burden, creates a degree of stakeholder confusion, and hinders easy program engagement and navigation.
- **A detailed review of how the EA program is managed within FDA pointed to additional, addressable opportunities.** Opportunities are related to (1) improving FDA’s public website content, (2) investing in resources to support patient/physician program navigation and (3) improving the systems (and data) used to manage the EA program.
- **Manufacturers report facing challenges particularly related to (1) uncertainty about how FDA uses data from EA, and (2) managing divergent requirements and guidance from ex-US health authorities.** Some manufacturers report perceived uncertainty around how data from the EA program will be interpreted and possibly affect investigational products either still under development or undergoing regulatory review, though recent studies suggest that drug development has not been harmed.<sup>7</sup> Global challenges cited related principally to divergent practices and requirements (e.g., investigational product labeling) across health authorities.

A more detailed discussion of the report’s findings can be found in Section 3.

FDA and the other stakeholders in the ecosystem could consider several steps to strengthen the EA program. The following are high-level recommendations for FDA and other stakeholders to consider, organized around four guiding principles. These reflect many recommendations from recent literature. Detailed recommendations for consideration are discussed in Section 4.

1. ***Ensure patients continue to receive timely and medically appropriate access to investigational medical products through the EA program.*** Recommendations center on strengthening dialogue with manufacturers about the EA program across the product development lifecycle.
2. ***Make participating in the program minimally taxing for stakeholders (physicians, patients, FDA, and others).*** For example, FDA can place greater emphasis on cross-pollinating known best practices (within FDA), to enhance stakeholders’ program experience.

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<sup>7</sup> Jonathan Jarow, Richard Moscicki, “Impact of Expanded Access on FDA Regulatory Action and Product Labeling,” *Therapeutic Innovation & Regulatory Science*, Volume 51, Issue No. 6 (2017): 1-3

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3. ***Make the program easy for patients, physicians, and other stakeholders to understand and navigate.*** Recommendations focus on clarifying program language, enhancing online resources, and building program awareness and understanding in the community care setting<sup>8</sup>
  4. ***Continue to integrate data from the program with medical product review to provide transparency and promote quality decision-making.*** Recommendations strive to help manufacturers understand how FDA may use data from EA and correct manufacturer misperceptions that data from EA harms product development, strengthen the use of data to manage and oversee the EA program, and further link EA data to the systems that support ongoing regulatory decision-making.

In summary, this report acknowledges and commends FDA on its efforts to manage and improve the EA program, facilitating rapid access to investigational therapies for patients in need while preserving the Agency's ability to make informed regulatory decisions that protect and promote the public health. The findings and recommendations discussed in the following sections are designed to further the Agency's public health mission through targeted program enhancements that have been informed by a broad range of healthcare ecosystem stakeholders.

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<sup>8</sup> In this report, the community care setting is defined as care delivered outside of an academic medical center (AMC) or AMC-affiliated facility. According to Joint Commission International, an academic medical center is integrated with medical school, offers education for medical students and postgraduate trainees, and is engaged in conduct human subject research.

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## Section 1: Background/FDA’s EA Program

### 1.1 Background

The U.S. Food and Drug Administration (FDA or “Agency”) regulates the development and approval for marketing of medical products in the United States of America (US) under authority from the Federal Food, Drug, and Cosmetic Act (FFDCA). For unapproved products, a clinical trial is generally the mechanism by which patients gain access to investigational products. However, in some cases, a clinical trial is not an option for a patient. In these cases, patients, in consultation with their physicians, may obtain access to unapproved therapies through FDA’s Expanded Access (EA) program.<sup>9</sup>

Since the 1970s, the U.S. Food and Drug Administration (FDA) has facilitated making investigational drugs available to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. The FDA’s Expanded Access (EA) process was formalized through regulation in 1987 (drugs and biologics)<sup>10</sup> and 1996 (devices)<sup>11</sup>, and EA was further codified in law in 1997<sup>12</sup>. The EA program provides a pathway for patients, acting through their physician, to obtain investigational new drugs, biologics or devices that would otherwise be unavailable outside of a clinical trial setting to address a serious condition or disease for which there are no satisfactory alternatives.<sup>13</sup> Over the past five years, FDA received approximately 9,000 EA requests and authorized 99% of those requests.

FDA is committed to continuous improvements and updates to the program. For example, FDA recently streamlined the required supporting documentation for EA requests for drugs and biologics, reducing administrative burden for sponsors (typically physicians) to complete the required form by about 90%, from 8 hours to 45 minutes. The Agency also simplified the requirements for IRB review for single patient EA requests for investigational drugs and biologics so that a single member, such as the IRB Chair, can provide concurrence rather than requiring full board approval, which promotes consistency across all EA programs.<sup>14,15</sup>

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<sup>9</sup> The EA program is sometimes referred to as the “compassionate use” program.

<sup>10</sup> Per 21 CFR 312 section I

<sup>11</sup> Per 21 CFR part 812

<sup>12</sup> FDA’s EA program is sometimes referred to as the “compassionate use” program. “Expanded access” involves use of an investigational medical product outside of a clinical trial.

<sup>13</sup> FDAMA.

<sup>14</sup> Scott Gottlieb, FDA Commissioner, “Expanded Access: FDA Describes Efforts to Ease Application Process,” FDA Voice. FDA, Original publication October 3, 2017, <https://blogs.fda.gov/fdavoices/index.php/2017/10/expanded-access-fda-describes-efforts-to-ease-application-process/> (accessed February 5, 2018).

<sup>15</sup> Expanded Access for Medical Devices, <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm> (accessed April 17, 2018).

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Additionally, FDA has released guidance on how it uses safety data generated from using an investigational drug or biologic through EA pathways.<sup>16</sup>

This independent assessment was undertaken in 2017 and 2018 to better understand the program’s current performance and identify areas for additional improvement. Because the EA program has multiple stakeholders, the assessment sought to build on existing reviews of the program by taking a comprehensive look at the healthcare ecosystem. Accordingly, the report integrates perspectives from patients and their advocates/caregivers, healthcare providers and the health systems that support healthcare providers, payers, IRBs, manufacturers, and FDA staff. The report presents many of these perspectives, and combined with quantitative and qualitative insights about program performance, identifies opportunities to strengthen the program. The report concludes with specific recommendations for FDA and other stakeholders to consider as they work to continually enhance this important public health program.

## 1.2 Report Focus—Obtaining Expanded Access

For clarity, this report focuses on applications (alternately termed “requests”) submitted to FDA to obtain access to investigational products through the EA program. The EA program (described in detail in Section 5) provides patient access to an investigational product (i.e., drug, biologic or device) outside of a clinical trial to treat or diagnose a serious or immediately life-threatening disease or condition in the absence of a comparable or satisfactory alternative therapy.<sup>17</sup>

Expanded access to drugs and biologics is authorized through the submission of a new protocol to either an existing or new investigational new drug application (IND). This can be for (1) a single patient, (2) an intermediate size patient population, or (3) a larger treatment population. These pathways are defined in the following way:

- A *single-patient protocol to a new or existing IND* is used to request treatment for a single patient.
  - When there is an emergency that requires treatment before a written submission can be made to FDA, the sponsoring physician may request and obtain authorization from FDA by telephone or other means of rapid communication.
  - The sponsor must then follow up with a written submission of the emergency protocol to a new or existing IND within 15 days of FDA’s authorization.
- An *intermediate-size patient population protocol to a new or existing IND* is used for more than one patient but a population smaller than the typical treatment protocol to a new or existing IND (discussed further below). This type of protocol may be used when the investigational drug or biologic is not being developed for marketing (e.g., if

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<sup>16</sup> FDA Center for Drugs Evaluation Research (2017). Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers (FDA Maryland).

<sup>17</sup> FFDCA 21 USC, Section 360bbb, “Expanded access to unapproved therapies and diagnostics,” [http://uscode.house.gov/view.xhtml?req=\(title:21%20section:360bbb%20edition:prelim](http://uscode.house.gov/view.xhtml?req=(title:21%20section:360bbb%20edition:prelim).

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development has been discontinued), or when the product is being developed but the sponsor is not yet actively pursuing marketing approval with due diligence.

- A ***treatment protocol to a new or existing IND*** is used for widespread treatment use or to bridge the gap between the completion of clinical trials and marketing of the product.

Investigational devices may be obtained through FDA’s EA program via three pathways: (1) emergency use, (2) single patient (also called “compassionate use” with or without an investigational device exemption [IDE]<sup>18</sup>), and (3) treatment IDEs. These pathways are defined in the following way:

- ***Emergency use*** is an immediate need, as determined by the physician, to use an unapproved device to treat life-threatening or serious diseases or conditions when there is no generally acceptable alternative and there is no time to obtain FDA approval due to the immediate need. Under these circumstances, the unapproved device may be used for treatment without prior notification to or approval by FDA. FDA expects the physician to make the determination that the patient’s circumstances meet these criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. If there is an existing IDE for the device, the IDE sponsor must notify the FDA of the emergency use within five days<sup>19</sup> through submission of an IDE report. If there is no IDE, the physician should submit a follow-up report to FDA describing the device used, patient’s outcome and the patient protection measures followed.
- ***Single patient use requests*** (also termed ‘Compassionate Use’) are those non-emergency situations for which expanded access to an unapproved device may be warranted for a single use. This mechanism is termed an “investigational device compassionate use request” and is either approved under an existing IDE or authorized when an IDE does not exist before treatment can begin. In rare circumstances, a small group access protocol may be considered under this pathway. Prior FDA approval is needed before such use occurs. If there is an open IDE for the investigational device, the request is submitted as an IDE supplement by the IDE sponsor. If not, the request may be submitted to FDA by the physician or manufacturer as a standalone request. The physician should not treat the patient identified in the request until FDA approves use of the device under the proposed circumstances.
- ***Treatment IDEs*** are applications for widespread use of an unapproved device to treat or diagnose a serious or immediately life-threatening disease or condition, and require prior FDA approval. The application may be submitted under an existing or as a new IDE.<sup>20</sup>

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<sup>18</sup> An IDE allows a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting a clinical investigation, 21 CFR 812.1.

<sup>19</sup> 21 CFR 812.35(a)(2), “Changes effected for emergency use,”

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.35>.

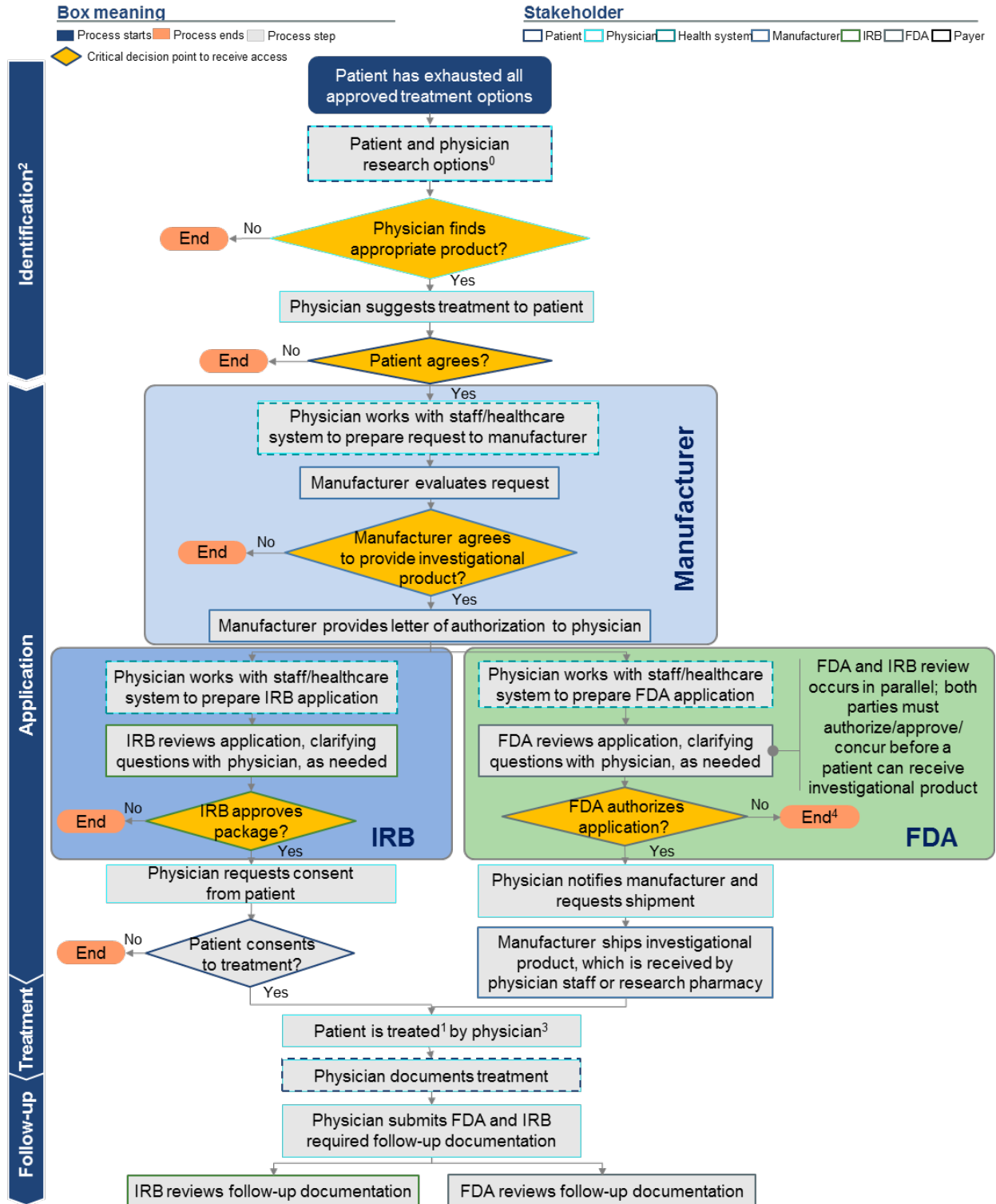
<sup>20</sup> 21 CFR 812.36.



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The high-level process for a “typical” EA request for a single patient, sponsored by a physician, is described in *Figure 1*, and in more detail in Section 5.

**Figure 1 – High level flow chart for a “typical” single patient EA request**



<sup>0</sup> Physician or patient may consult manufacturer EA policies, in addition to seeking/receiving information from payers, manufacturers and FDA to complete required application documentation

<sup>1</sup> "Treatment" in this case could include the use of a diagnostic device, or any other use of investigational medical product

<sup>2</sup> Phases described in Section 5.2

<sup>3</sup> If physician is affiliated with a health system, the system typically coordinates any appropriate billing; payer may reimburse the cost of professional fees related to administration and any associated complications, subject to payer coverage policies

<sup>4</sup> The application can alternatively be placed on hold and subsequently authorized if the physician provides an adequate response to FDA

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Facilitating patient access to investigational products is a delicate undertaking that involves complex ethical, medical, and legal judgments. This report does not address those aspects of the program. Nor does the report discuss other pathways, including Personal Importation (in which a patient imports a medical product for personal use either in personally transported baggage or shipped by courier)<sup>21</sup> or Emergency Use Authorization (EUA) (which allows the broad use of an investigational medical product in response to a public health emergency).<sup>22</sup>

### **1.3 Report Organization**

Following a brief description of the objectives and methodology used during the assessment, this report presents the findings (see Section 3) and recommendations (see Section 4). To clarify what can be a complicated process, Section 5 describes the roles of stakeholders and the process for a “typical” EA request.

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<sup>21</sup> Personal Importation. <https://www.fda.gov/ForIndustry/ImportProgram/ImportBasics/ucm432661.htm> (accessed April 16, 2018).

<sup>22</sup> EUA. <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm> (accessed April 16, 2018).

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## Section 2: Objectives and Methodology

This report presents the findings of an independent assessment of FDA’s EA program that was conducted on FDA’s behalf. The research objectives and approach undertaken are described in this section. More detailed information is available in the “Expanded Access Program Report: Addendum” document.

### 2.1 Research Objectives

The following objectives guided the assessment:

- Assess the current performance of FDA’s EA program; conduct analyses to establish a baseline for the program, and identify areas for improvement
- Evaluate the experience of physician sponsors and best practices across interactions with FDA and opportunities for improvement
- Convene stakeholders across the broader healthcare ecosystem to assess knowledge, interest, and use of the EA program, and form recommendations to improve awareness
- Perform a user experience assessment of EA webpages focused on three websites: FDA.gov, ClinicalTrials.gov, and Reagan-Udall Foundation’s EA Navigator
- Make recommendations to improve the overall EA program, including identifying where FDA can directly affect change

### 2.2 Research Methodology

The findings and recommendations in Sections 3 and 4 resulted from extensive research involving a broad range of inputs, both quantitative and qualitative. The following is a brief description of those sources:

- ***In-depth review of FDA-focused written materials*** – Relevant statutes (e.g., FDCA Section 561), Code of Federal Regulations (CFR) (e.g., 21 CFR parts 312 and 812), FDA Manual of Policies and Procedures (MAPPs) and Standard Operating Policy and Procedures (SOPPs), guidance documents, job aids, and review articles
- ***Historical data*** – FDA-housed data from 2012 to 2016 on volume of applications, authorization or approval rate, and timeliness of review from each of the three medical product centers
- ***Interviews with FDA experts*** –34 FDA staff with direct experience handling EA requests
- ***Interviews with external stakeholders*** –29 interviews were conducted with physicians and health systems leaders, patients and patient advocacy groups, IRB representatives, and payer representatives (both public and private sector)
- ***Focus groups with external stakeholders*** – Five focus groups with nine patients or representatives of patient advocacy groups

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- ***Survey of previous EA applicants*** – A survey of physician sponsors who submitted at least one EA application to FDA between 2011 and 2017, with 139 respondents
  - ***Evaluation of externally-facing websites*** – Formal user-centered design assessment of primary websites providing EA information (FDA homepage for EA<sup>23</sup>, ClinicalTrials.gov<sup>24</sup>, and Reagan-Udall Foundation’s EA Navigator<sup>25</sup>), complemented with Google Analytics website traffic data (e.g., number of visitors, search terms, navigation to and from the home page, and time spent on the page) from January to October 31, 2017
  - ***Social media listening*** – Raw user-generated posts from a wide variety of sources (e.g., Facebook, Twitter, patient fora), leveraging relevancy filtering and scoring to categorize population segments and extract directional insights around attitudes and sentiments on EA
  - ***Analysis of incoming responses to CDER’s Division of Drug Information*** – Top questions about EA that CDER’s Division of Drug Information (DDI) received between January 2016 and November 2017, categorized by demographic

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<sup>23</sup> <https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>.

<sup>24</sup> <https://clinicaltrials.gov/>.

<sup>25</sup> <http://navigator.reaganudall.org/>.

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## Section 3: Findings

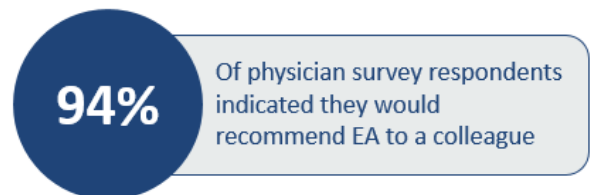
This section focuses on pain points identified in the assessment and on articulating opportunities for improvement. The principal findings were informed by a thorough, multi-stakeholder analysis and a careful evaluation of recent literature on the FDA EA program.

What follows is a summary of the main findings from the research conducted to generate this report, including a brief discussion of evidence supporting each finding.

### **Finding 1: External stake-holders’ overall perceptions of the EA program—and FDA’s role in particular—are positive.**

These perceptions are from stakeholders across the healthcare ecosystem, and they echo findings in the recent GAO report<sup>26</sup> as well as numerous sources in the broader literature. See the “Expanded Access Program Report: Addendum” document for an in-depth discussion of stakeholder experience and insights from their participation in the EA program.

Physicians, especially those with direct experience submitting an EA application to FDA, reported positive impressions of the program. A survey of 139 physicians with direct experience submitting an EA application to FDA was conducted for this report and 94% of respondents reported a willingness to recommend the program to a colleague. Several cited specific staff members at FDA who educated them on the EA process and provided input on their proposed protocol. Those interviewed (a group distinct from survey respondents) consistently agreed that FDA’s EA program is important for patients without other options who may benefit from investigational treatment.



Similarly, patients and their advocates described the program as a crucial route to access investigational therapies when other alternatives have been exhausted. Those with direct prior experience (as patients, advocates, or caregivers) reported positive experiences with the EA program in focus group discussions and in social media posts. Advocacy groups shared numerous examples of individuals and groups of patients receiving access to lifesaving investigational products when approved therapies were unsuccessful and the patients were otherwise ineligible for clinical trials. However, many advocacy groups underscored the importance of ensuring that the EA program does not hinder ongoing investigational product development (e.g., by diverting enrollment from clinical trials) and noted that this consideration was important in their tendency to support the program.

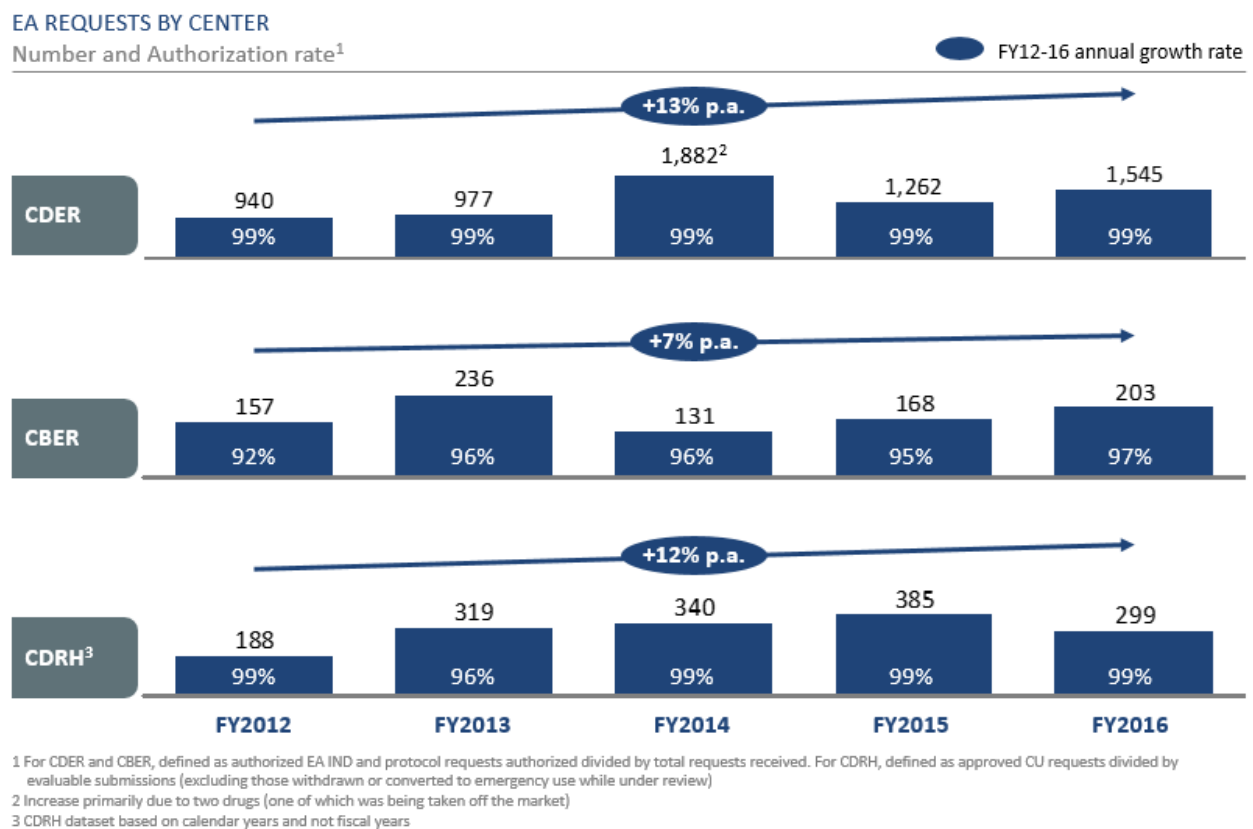
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<sup>26</sup> U.S. Government Accountability Office, *Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used*, July 11, 2017, GAO-17-564, Washington, D.C.: U.S. Government Accountability Office.

Manufacturers, patient advocates, IRB representatives, and physicians all noted that FDA has taken important steps to reduce the administrative burden associated with submitting requests and seems genuinely committed to facilitate medically appropriate access via the EA program. Several physicians interviewed pointed to the significantly streamlined application Form 3926, which is available for physicians to use for expanded access requests for single patient INDs in CDER and CBER, while others lauded efforts by the Office of Health and Constituent Affairs (OHCA) and certain divisions to engage with the public and educate the community about the EA program and how to most effectively navigate it.

Over the last four years, the EA program’s application volume has grown consistently across all three centers, with FDA receiving approximately 1,800 applications on average annually for the past five years. **Figure 2** shows the growth in requests across centers for EA from 2012 to 2016.

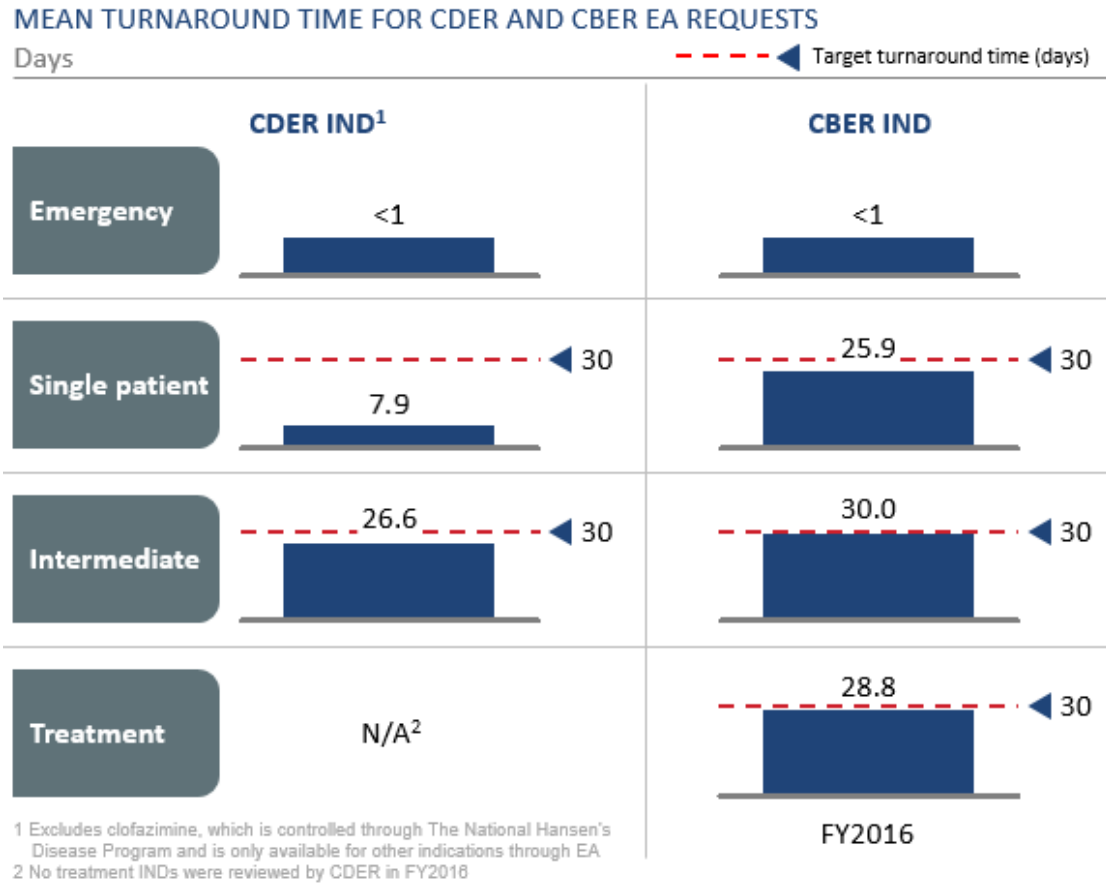
**Figure 2 – EA requests for CDER, CBER and CDRH**



Despite double-digit growth in volume, FDA’s review timelines consistently meet or exceed target turnaround times. Emergency requests for single patients are regularly reviewed by CDER and CBER in less than one day (in CDRH, emergency use does not require prior notification or authorization). Non-emergency requests for single patients take longer, between 8 days and 26 days, depending on the center, against a target turnaround of 30 days. Intermediate-size patient population and treatment IND or protocol requests had a review duration in-line with typical IND review processes (i.e., less than or at 30 days). Treatment IDEs are rarely used for EA and

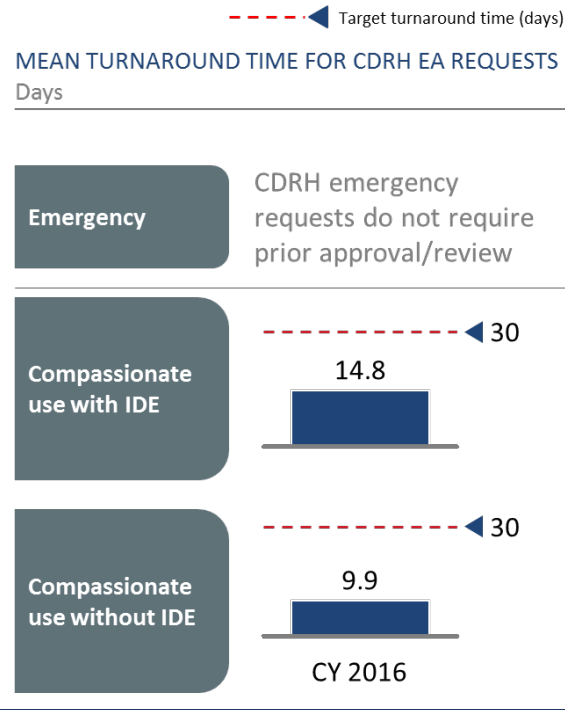
are excluded from this analysis. **Figure 3** and **Figure 4** show the turnaround time in days by center for each type of EA request.

**Figure 3 – Turnaround time for CDER and CBER EA requests**





**Figure 4 – Turnaround time for CDRH EA requests**

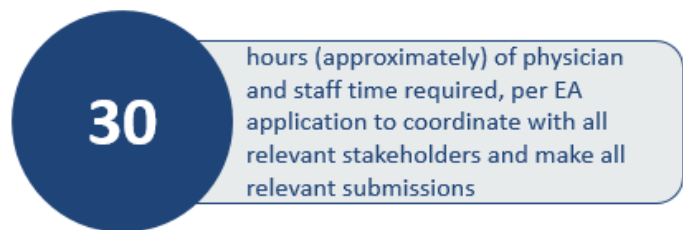


**Finding 2: Stakeholders report pain points across the physician/patient journey, which, if addressed, could meaningfully enhance the program.**

The reported pain points varied significantly based on the respondent’s experience with the program, but what follows is a summary of areas consistently identified by stakeholders as exhibiting potential for improvement:

**1. Program awareness.** Awareness of the EA program, especially in the community-based care setting (i.e., outside of an academic medical center), is low. This is further compounded by the relative absence of administrative personnel in the community setting with experience and knowledge to support application submission. This observation correlates with lower levels of participation in clinical research—interviews revealed that physicians who were not involved in clinical trials were often less aware of the newest therapies and less likely to have exposure to those stakeholders (manufacturers, IRBs, and FDA) that play a vital role in facilitating EA.

**2. Administrative burden.** Without dedicated staff to support clinical research, the administrative burden to apply for EA and comply with required monitoring and reporting falls on physicians and their administrative staff.

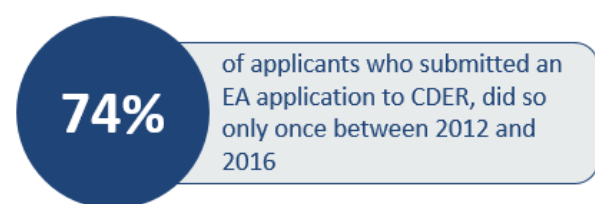


Paperwork is reported to be the key hurdle, particularly for IRB approval and requesting manufacturer access to an investigational drug, biologic or device. Surveyed physicians estimated that the total time required to support an EA application (including submissions to all

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relevant stakeholders and other required coordination) can average nearly 30 hours for a single application (17.1 hours for the physician and 12.5 hours for his or her staff), which is not reimbursed by payers or other parties. Several stakeholders interviewed suggested that differences in working familiarity with EA applications and in resources available to support applications between academic and community settings of care drives disparity in access to investigational therapies through EA.

**3. Program navigation.** Stakeholders indicated that navigating the program was challenging, especially for physicians without prior experience. All physicians who have undertaken EA applications on behalf of their patients (regardless of setting) cited challenges associated with



coordinating applications across the multi-step, multi-stakeholder process. The challenge of navigating the program was especially acute for first-time applicants.<sup>27</sup> Survey respondents who had filed only one application reported more difficulty working with the manufacturer to

request access and receive the product, finding and engaging an IRB to obtain approval, and completing required documentation during and after treatment. Interviews and survey responses consistently mentioned frustration with the necessity of coordinating with multiple stakeholders, i.e., the manufacturer, the IRB, FDA, the health system, and a patient's insurance company.

**4. Program informational resources.** Respondents provided feedback that improvements are needed in the resources available on public websites that support the EA program. Specifically, stakeholders expressed frustration with the lack of richness, reliability (i.e., that the information is accurate and up-to-date), and accessibility of information available through FDA websites. Although many cited the convenience of the CDRH website, stakeholders who interacted with the CDER and CBER materials noted the absence of a single location to retrieve relevant program information.

Respondents also reported difficulty navigating to the required information; even FDA staff reported relying on a search engine to find specific information or materials rather navigating through the Agency's internal resources. FDA's webpages are long—some require 10 to 15 minutes to read while website traffic analytics showed only an average of three minutes spent on FDA's EA home page, suggesting limited engagement. Moreover, the EA home page averages a bounce rate<sup>28</sup> of 62%, which suggests that when users search and land on the page, they are not finding what they need. In addition, Form FDA 3926 is inaccessible in many common web

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<sup>27</sup> Estimated to be approximately 74% of physician sponsors, according to an analysis of FDA data.

<sup>28</sup> This is typically the percentage of visitors to a website who navigate away (bounce away) from the site after viewing only one page.

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browsers.<sup>29</sup> In fact, requesting the form because it was not available through the website was the second most common EA-related question CDER’s DDI received across all demographics.

Physicians, payers, and patient groups cited the importance of the National Institutes of Health (NIH) website, ClinicalTrials.gov<sup>30</sup> (which includes information about EA programs from manufacturers), in identifying treatments available through EA. Recent improvements to the ClinicalTrials.gov site, such as queries linking search terms like expanded access, compassionate use, and pre-approval access, have simplified the identification step. Physicians not already engaged in research with industry contacts cited the criticality of having EA-related information available in a central, searchable database. While manufacturers are required to submit information about their EA programs for drugs and biologics, including contact information, to ClinicalTrials.gov<sup>31</sup>, several stakeholder groups reported that navigating the site to view product availability through EA is difficult.

Representatives from patient advocacy groups familiar with the Regan-Udall Foundation Expanded Access Navigator<sup>32</sup> agreed that the website is a helpful resource. However, awareness was not universal. The anticipated expansion beyond oncology will likely increase awareness among patient groups focused on other therapeutic areas.

Separately, a formal usability analysis of FDA.gov, ClinicalTrials.gov and the Reagan-Udall Foundation Expanded Access Navigator, using heuristic evaluation was conducted. This evaluation benchmarked the sites against a validated framework of 12 industry-standard usability heuristics. The analysis evaluated website experience through the lens of three main visitor profiles—patients, health care personnel (HCP) and industry representatives—that potentially interact with these websites to gather information and complete tasks related to the EA program. While the analysis has findings specific to each website, it identified consistent opportunities to improve the ease of navigating the websites, enhance clarity and usability of provided information, and provide access to user help and support. For additional details, see the “Expanded Access Program Report: Addendum” document.

**Finding 3: Because EA operates in an inherently multi-stakeholder environment, the absence of standard processes and policies for EA submission requests to FDA, manufacturers, IRBs, and payers creates confusion for many stakeholders.**

Physicians repeatedly cited challenges with differences in application requirements for submission to FDA, manufacturers, IRBs, and payers, which drive substantial administrative workload for the physicians and their staff. Physicians interviewed pointed to the difficulty of

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<sup>29</sup> There are instructions on how to access the form at the top of the FDA forms page where the form is housed (<https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>). However, this text can be missed if the form is accessed directly through search results.

<sup>30</sup> <https://clinicaltrials.gov/>

<sup>31</sup> Per 42 CFR 11.28

<sup>32</sup> <http://navigator.reaganudall.org/>

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identifying the correct contact for each manufacturer and the process for submitting a request. Furthermore, survey respondents cited manufacturer denial as the most frequent reason for not submitting an EA application to the Agency where the request was previously submitted to the manufacturer.

For physicians practicing in a setting without ready access to an IRB, the process of identifying an IRB and covering the cost of an application, while often waived by the IRB, was frequently identified as a challenge by physicians and patient advocates alike. Since each IRB sets its own internal process, working with multiple IRBs requires the physician to learn a new process for each one. Physicians reported that IRBs that do not regularly review EA requests occasionally ask for supporting documentation that is not feasible in an EA setting (e.g., data that does not exist or is not available in a timely manner). IRB interviewees reported that unlike applications related to a manufacturer-sponsored trial (with standard forms and templates), they saw physicians struggle to develop the required documentation.

There is also substantial variability in cost coverage from payers for treatments administered via EA. Although the investigational product itself is typically provided by manufacturers at no cost, interviews and published literature indicate that there is often associated expense for treatment administration and for monitoring progress and complications. Many payers (both public and private) report that they cover this associated care, but almost always on a case-by-case basis and often in accordance with clinical trial coverage policy, which can vary from standard coverages. According to the patient advocates who participated in focus groups, these varied policies cause financial uncertainty for patients who have often exhausted all other resources before becoming eligible for EA. Inconsistencies in policy also frequently require the physician or administrative staff to spend additional time engaging with payers to provide additional documentation and secure authorization.

**Finding 4: A detailed review of how the EA program is managed within FDA pointed to additional addressable opportunities.**

Interviewees from across the stakeholder spectrum consistently cited confusion in terminology as a primary barrier to understanding and effectively researching the EA program. For example, the terms “expanded access” and “compassionate use,” often used to refer to the EA program, mean different things to different stakeholders. The respondents said inconsistent terminology and definitions has created challenges in discussing topics with colleagues and introduced confusion about program intent and potential eligibility. Some patient advocacy groups reported that unclear definitions caused them to incorrectly assume that their communities did not have access to the program, for example, not understanding that the EA pathway can be used for treatment of a serious but not immediately life-threatening condition.

Best practices and adaptations to enhance program effectiveness exist across FDA centers and divisions within centers, but are not systematically cross-pollinated to share learnings and elevate program execution. FDA’s recently established Expanded Access Coordinating Council (EACC) is an important first step toward formalizing a venue for sharing those practices, but more can be done to raise awareness of center- and division-level innovations and identify ways to

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systematically apply them. For example, teams within FDA have built robust and efficient processes for facilitating and reviewing requests, such as offering packets of information with detailed instructions, pre-populated template materials, and previously used protocols. However, standardization of the process should not be the primary goal—much of the observed variability is appropriate for the wide range of products regulated and makes the process nimble and efficient.

Finally, the richness and quality of data available to FDA—both on EA program performance and impact, and data related to outcomes—are highly variable across centers. Given (1) limitations in current systems and staff capacity, (2) modest availability of standard queries/reports, and (3) the scope of training for review teams, it is difficult to access and analyze data about EA. This variability complicates developing a comprehensive, timely picture of program performance and consistent, transparent program management. The variability also prevents FDA from routinely publishing facts about the program’s impact on public health, an activity that could help address persistent misunderstandings about the EA program.

**Finding 5: Manufacturers report facing challenges particularly related to (1) uncertainty about how FDA uses data from EA, and (2) managing divergent requirements and guidance from non-FDA, ex-US health authorities.**

A commonly reported, yet unsubstantiated, concern by manufacturers is that data from an EA program could derail ongoing product development or compromise regulatory review. This



concern was widespread among manufacturers interviewed, despite updated guidance on use of data for EA for drugs and biologics released in October 2017<sup>33</sup> that states that the data are considered in context,<sup>34</sup> and despite literature showing that there have been no instances in which EA has led to a negative regulatory

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<sup>33</sup> FDA CDER (2017). Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers (FDA Maryland).

<sup>34</sup> From the FDA CDER (2017). Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers: “FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted and will evaluate any adverse event data obtained from an expanded access submission within that context. For example, FDA reviewers recognize that: 1) expanded access treatment generally occurs outside a controlled clinical trial setting; 2) patients who receive a drug through expanded access may suffer from a more advanced stage of the disease or condition than patients participating in a clinical trial; 3) patients who receive a drug through expanded access may be receiving other therapies for their disease or condition at the same time as the drug they are receiving through expanded access; and 4) patients who receive a drug through expanded access may suffer from one or more comorbidities. All these factors make it difficult to link an expanded access treatment to a particular adverse event. Moreover, it is very rare for FDA to place an IND on clinical hold due to adverse events observed in expanded access treatment.”

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decision regarding a drug application.<sup>35</sup> Nevertheless, this uncertainty is cited as a top consideration for manufacturers' participation in EA, even by companies experienced with the program. For those that do participate, interviews surfaced a wide range (40% to 95%) of manufacturer approval rates for EA requests.

Variations in policies across geographies and other non-FDA global health authorities add major complexity for manufacturers when seeking to remain compliant in responding to EA requests. Because countries have different regulations and importation requirements (for investigational products shipped across borders), manufacturers must track and comply with a challenging array of requirements (manufacturers especially mentioned variations in labeling requirements from country to country as a logistical challenge).

Manufacturers also worry about how to navigate the line between publicizing their EA participation and any perception that they are marketing an unapproved product. Manufacturer interviewees frequently mentioned the difficulty with managing the tension of wanting to inform physicians whose patients could potentially benefit while remaining compliant with regulations governing the information that can be shared.

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<sup>35</sup> Jonathan Jarow, Richard Moscicki, "Impact of Expanded Access on FDA Regulatory Action and Product Labeling," *Therapeutic Innovation & Regulatory Science*, Volume 51, Issue No. 6 (2017): 1-3.

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## Section 4: Recommendations for FDA and Other Stakeholders to Consider

As the preceding analysis outlines, the EA program operates in a complex, multi-stakeholder environment. As such, addressing a number of the identified pain points (e.g., policy inconsistency, application burden) requires coordinated action on the part of a number of disparate stakeholders. What follows below is a set of recommendations for FDA to specifically consider, framed around actions that are within FDA's remit to take if it chooses. Those recommendations are grouped around four broad principles to guide continuous improvement activity for the EA program moving forward.

***Principle 1: Ensure patients continue to receive timely and medically appropriate access to investigational medical products through the EA program.***

**Recommendation 1: Consistently incorporate EA planning into manufacturer interactions.**

FDA could consistently engage with manufacturers on EA throughout the medical product development lifecycle to proactively assess and plan for potential EA applications, as appropriate. In many cases, FDA can anticipate circumstances when a product might be subject to an EA request. Such discussions could have numerous benefits, such as:

- Supporting the development of robust, publicly accessible, product-level manufacturer policies for granting EA requests
- Prompting a dialogue that encourages planning for EA use (e.g., securing sufficient clinical supply), without compromising the critical importance of clinical trials
- Prospectively clarifying how data from EA might be used prior to and during application review

The process could also facilitate more systematic identification of appropriate opportunities to use intermediate and treatment protocols (for drugs and biologics), and treatment IDEs (for devices). This may enable more timely access for patients, provide more robust data collection and monitoring, and reduce the administrative burden for all stakeholders. In the short term, review teams could pilot such conversations to explore what types of discussions are most helpful, with a long-term goal of standardized questions posed to manufacturers as part of sponsor interactions, as appropriate.

***Principle 2: Make participating in the program minimally taxing for stakeholders (physicians, patients, FDA, and others).***

**Recommendation 2: Systematically cross-pollinate best practices in FDA program execution and management.** FDA could build on existing mechanisms, such as the EACC, to systematically cross-pollinate best practices to enhance program execution and management. Given that FDA is a de-centralized organization, intentionally seeking out and formalizing approaches to disseminate best practices in EA program execution and management across centers and divisions is essential.

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One example of an innovation that could be leveraged more broadly is the use of packets for frequently requested products. This may reduce administrative burden on physician sponsors and streamline the review of these applications. These packets include specific, step-by-step instructions on how to submit an EA application, along with a previously reviewed protocol and form with specific completion instructions. Physicians retain the ability to propose alternative protocols; however, these require additional review by FDA staff to ensure the risk-benefit profile is acceptable.

***Principle 3: Make the program easy for patients, physicians, and other stakeholders to understand and navigate.***

**Recommendation 3: Clarify language used to describe the program, both internally and externally.** By unifying the language (ideally for all centers) and choosing consistent terminology when communicating with external stakeholders, FDA can foster a broad and clearer understanding of the program.

**Recommendation 4: Enhance the use of EA in community medical centers through a systematic campaign to educate physicians and administrative personnel.** Addressing the lack of program awareness and limited understanding about the process among physicians will help to overcome a major barrier to EA in the community setting. While FDA will need to assess the most effective methods to build awareness and working familiarity with the EA program in the community setting, the following are examples of possible initiatives:

- Routinely presenting on the EA process at conferences organized by national societies, such as the American Society of Clinical Oncology (ASCO), the American Academy of Neurology (AAN), Infectious Diseases Society of America (IDSA), and selected regional conferences.
- Delivering continuing medical education (CME) webinars in partnership with national societies and larger CME providers (e.g., MedScape).
- Implementing an outreach campaign (e.g., FDA blogs) to build awareness with stakeholders and share known best practices with community health system administrators on how to support EA applications with limited resources.

**Recommendation 5: Conduct a user-centered redesign of web-based materials.**

Organizations involved in Expanded Access, including the FDA, National Institutes of Health (NIH), and the Reagan-Udall Foundation, could conduct user-centered redesigns of their Expanded Access web-based materials to enhance their relevance and impact. Redesigns could incorporate common features, as appropriate, to create a more consistent and easy navigation experience across the websites that support EA program engagement. Specific website-related recommendations, with a detailed discussion of the website analysis, findings, and suggestions, are available in this report's addendum. Two near-term improvements FDA could make are fixing Form 3926 so it can be accessed from all popular web browsers, and offering step-by-step instructions on the FDA webpage on how to navigate the ClinicalTrials.gov site and interpret search results for EA. In the long-term, a mobile device app for physicians may be useful in preparing, submitting, and tracking EA applications.



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**Recommendation 6: Invest in the development of a central navigation and triage resource for EA applicants.** Given the significance of EA application volume originating from physicians with limited EA program experience, a central navigation and triage capability at FDA that could interact with patients and physicians seeking information about how to engage with the EA program would be valuable. This system could facilitate connections to subject matter experts in the Centers when product or disease-specific questions or needs arise. It would serve as the “single point of entry” many stakeholders asked for, though would not replace existing connections stakeholders have within the Agency.

***Principle 4: Continue to integrate data from the program with medical product review to provide transparency and promote quality decision-making.***

**Recommendation 7: Correct manufacturer misperceptions that data from EA harm product development.** By bringing manufacturer attention to the recently released official agency guidance for drugs and biologics, FDA could increase manufacturer confidence that all data will be appropriately considered (i.e., in the context of an uncontrolled population, likely with advanced disease, and with many comorbidities), decreasing their reluctance to participate. Furthermore, FDA could clarify in the CDRH EA resources that in the absence of device-specific guidance, reviewers will generally follow drug and biologic guidance, if appropriate. In the long term, FDA could develop guidance specific to devices. In addition, the Agency could clarify which circumstances would be appropriate for EA data to support label extensions or other claims, potentially changing how manufacturers view participation in the EA program.

FDA could also consider providing the industry guidance on how manufacturers can build awareness of their own EA programs while avoiding any challenges related to marketing unapproved products.

**Recommendation 8: Ensure that FDA review staff are able to link EA applications within regulatory systems so program data is more easily and appropriately considered in regulatory decision-making.** FDA’s complex data architecture makes it challenging to link multiple INDs or other requests from physician sponsors to the manufacturer’s IND/IDE or pending marketing applications. Updating center systems to support EA application processing is a longer-term solution. In the near-term, providing review teams with additional training on system capabilities and creating standard reports that pull data from the existing systems and include all associated EA use could be near-term workarounds.

**Recommendation 9: Develop a common mechanism for tracking EA applications that enables each center to more actively manage the program.** Medical product centers should have accessible, near real-time data on application volume, timelines, origin of requests, disposition, and products involved in EA. In addition to giving FDA greater transparency into program performance, such tracking and reporting would also help FDA communicate more effectively to external stakeholders about program performance and the public health impact of the program. Program performance could be further communicated to stakeholders through periodic public meetings or publication of a brief annual report.

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While many recommendations may take several years to realize their full impact, FDA has the opportunity to begin work against all the recommendations in the relatively near term. Across all recommendations, opportunities to consider for near-term potential impact include: (1) beginning to pilot conversations with manufacturers about EA where appropriate, (2) clarifying the terminology used to describe the EA program in FDA’s web-based resources, (3) posting instructions on how to navigate ClinicalTrials.gov, (3) fixing Form FDA 3926 so it is accessible from all web browsers, (4) publicizing the October 2017 CDER/ CBER guidance on the use of data from EA for drugs, (5) clarifying in the CDRH EA resources that in the absence of device-specific guidance, reviewers will generally follow drug and device guidance, if appropriate (6) improving FDA reviewer training on system capabilities, and (7) creating standard reports of operational data to aid program management.

*Figure 5* summarizes the recommendations and the findings they address.

**Figure 5 – Mapping of recommendations to the findings they address**

		Findings								
		1	2	3	4	5				
		External stakeholders' overall perceptions of the EA program—and FDA's role in particular—are positive	Stakeholders report pain points across the physician/patient journey, which, if addressed, could meaningfully enhance the program	Because EA operates in an inherently multi-stakeholder environment, the absence of standard processes and policies for FDA, manufacturers, IRBs, and payers creates confusion for many stakeholders	Manufacturers face challenges, particularly related to (1) uncertainty about how FDA uses data from EA, and (2) managing divergent requirements and guidance from non-FDA, ex-US health authorities	A detailed review of how the EA program is managed within FDA pointed to additional addressable opportunities				
Recommendations		N/A								
<b>PRINCIPLE 1:</b> Timely/medically appropriate access	1 Incorporate EA planning into manufacturer interactions						✓		✓	✓
<b>PRINCIPLE 2:</b> Minimally taxing process	2 Systematically cross-pollinate best practices in FDA program execution and management						✓	✓		
<b>PRINCIPLE 3:</b> Easy program to understand and navigate	3 Clarify language used to describe the program, both internally and externally						✓	✓		✓
	4 Enhance the use of EA in community medical centers through a systematic campaign to educate physicians and administrative personnel						✓	✓		
	5 Conduct a user-centered redesign of web-based materials						✓	✓		
	6 Invest in the development of a central navigation and triage resource for EA applicants						✓	✓		
<b>PRINCIPLE 4:</b> Program data integration with product review	7 Enhance manufacturer understanding of how safety and efficacy data from EA may be used in regulatory decision-making							✓	✓	
	8 Ensure that FDA review staff are able to link EA applications within regulatory systems so program data is more easily and appropriately considered in regulatory decision-making									✓
	9 Develop a common mechanism for tracking EA applications that enables each center to more actively manage the program				✓					

## Section 5: Snapshot of the Stakeholder Roles and the EA Process

### 4.1 Stakeholder Roles

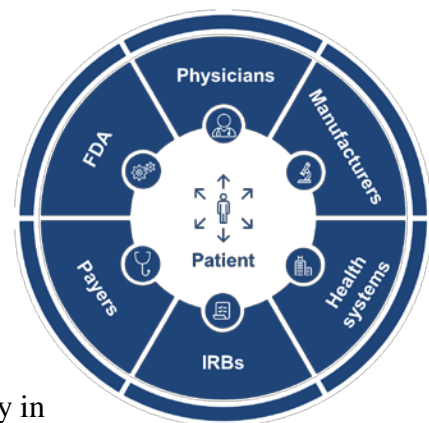
The process of obtaining access to investigational products via the FDA’s EA program requires interaction among seven principal stakeholders: FDA, patients, physicians, manufacturers, IRBs, and payers, and health systems. The following are high-level descriptions of the role each stakeholder plays in relation to an EA application. Additional detail is available in the addendum to this report.

#### FDA

FDA staff are involved in EA work across the Agency, including in CBER, CDER, and CDRH and in the Office of the Commissioner (OC). FDA fields inquiries from patients, healthcare providers, and manufacturers on the EA program. Once a healthcare provider or manufacturer submits an application, FDA works with the sponsor (i.e., the submitting physician or manufacturer) to triage, coordinate, review, and authorize the request. This can involve back-and-forth discussion with the sponsor. After a patient is treated, FDA receives reports on progress and safety, and considers that information in the context of the ongoing development program, as needed.

#### Patients

This analysis considers patients to be all patients who are prospective, current, or former users of FDA’s EA program. Their caregivers are also included in this group for the purposes of this report. Patients participating in the EA program have a life-threatening or serious condition, have exhausted all other approved treatment options, and do not qualify for participation in or have access to ongoing clinical trials for their condition. There is wide variation across patient populations in the level of knowledge, empowerment, and savvy in navigating the healthcare system. Their interactions with other program stakeholders is illustrated in *Figure 6*



**Figure 6 – Patients' view of the EA program stakeholder**

#### Physicians

Licensed physicians are responsible for treating patients and play a central role in identifying appropriate treatments and coordinating the required interactions across stakeholders to obtain treatment through the EA program. Physicians who interact with the program come from a wide range of specialties, the most common being hematology/oncology, infectious disease, and pulmonology. Physicians work in a range of settings, though it is estimated that as many as 95%

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of physicians that submit EA applications are in an academic setting as opposed to a community-based practice (based on the physician survey).

### **Manufacturers**

For this assessment, a manufacturer is the owner of the drug, biologic or device that is being requested for EA use. Manufacturers range from large, multinational pharmaceutical companies, to small biotechnology startups, to individual researchers in an academic setting. They differ markedly in terms of available resources (both financial and other types of resources), level of experience with the EA process, and relative progress in the development process (e.g., early stage, awaiting marketing approval). Manufacturers do not have a legal obligation to provide medical products through EA; however, in compliance with the 21<sup>st</sup> Century Cures Act, manufacturers of investigational drugs for serious diseases must publicly post their company policy for EA. The policy includes contact information, the process to make a request, and the criteria for consideration of the requests. Manufacturers can also post this information on the Reagan-Udall Expanded Access Patient Navigator website. FDA cannot compel a manufacturer to provide an unapproved medical product through the EA program.

### **IRBs**

Per 21 CFR part 56.102, an IRB is any board, committee or group formally designated by an institution to review, approve initiation, and conduct periodic reviews of biomedical research involving human subjects. The primary purpose of the reviews is to assure the protection of the human subjects' rights and welfare. An IRB can be associated with a hospital or academic institution or a private organization. The requirements and other expectations for the IRB's role in the use of an unapproved medical product through the EA process are described by the FDA regulations and institutional policies.

### **Payers**

Payers are private healthcare insurance companies and public insurance programs (e.g., Medicare, Medicaid, and Veterans Health Administration [VHA]) that may or may not cover the costs associated with treatments administered under EA. Each payer sets coverage policies for treatment costs, which may include professional fees for administration and subsequent monitoring, IRB review of the protocol, treatment of complications, and in some cases, the cost of the investigational product.

### **Health systems**

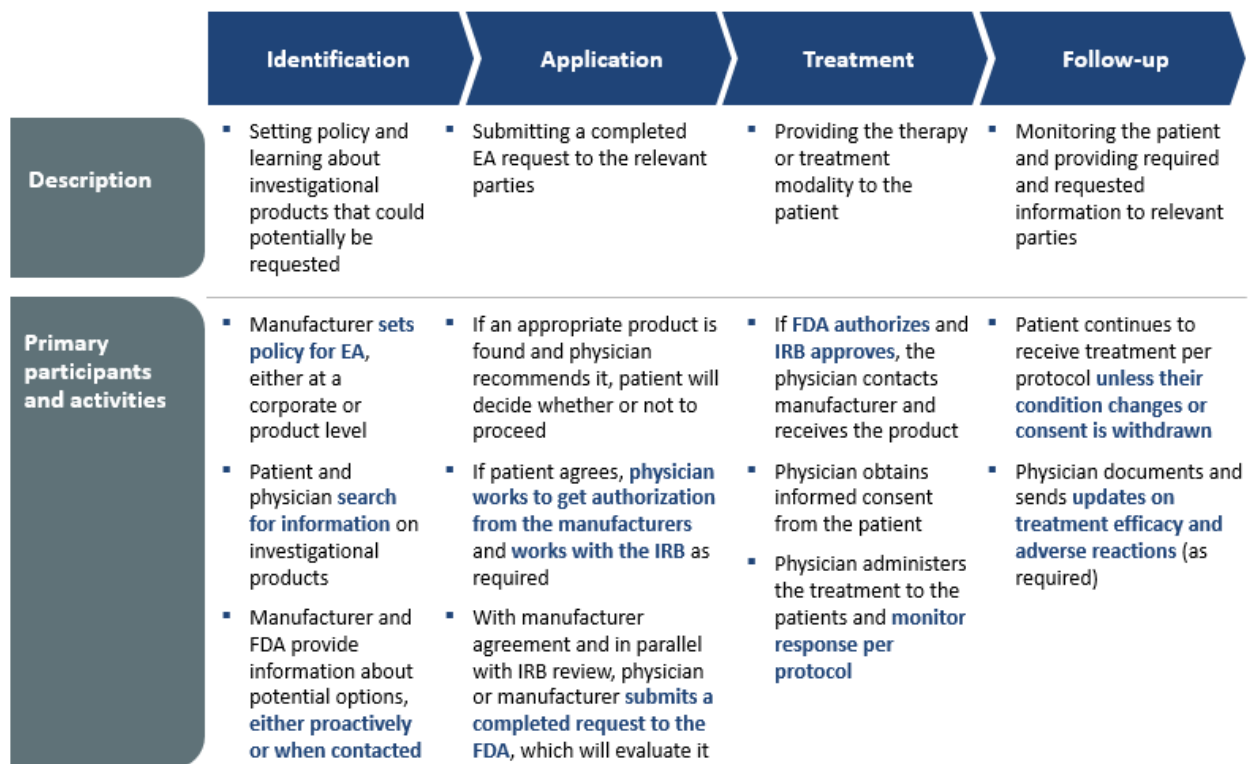
Health systems typically play a supportive role in EA and can play a significant role in supporting a physician sponsor. Health systems can be academic medical centers, community-based hospitals, or outpatient settings of care. They may include system administrators who set policy and manage a physician's practice; clinical research staff, including pharmacists and research coordinators; and the support staff who help physicians with administrative tasks. The health system typically provides infrastructure for administrative support, and may operate a research pharmacy to manage shipments of investigational medical products for hospitalized

patients. They also coordinate billing for any eligible procedures carried out in concert with administering the investigational therapy.

## 4.2 Process

At a very high level, the process of obtaining an investigational product through the EA program has four main steps: (1) identification, (2) application, (3) treatment, and (4) follow-up. Specific aspects of each step vary based on the type of product being requested, the FDA center reviewing the application, and the type of EA application submitted. **Figure 7** shows the high-level EA process steps with the associated participants and activities.

**Figure 7 – High-level view of the EA process**



This process is most representative for a single patient request initiated by a physician, i.e., a single patient protocol to a new or existing IND (for a drug or biologic) or compassionate use without an IDE (for a device).<sup>36</sup> The following is a description of each process step.

### Step 1: Identification

<sup>36</sup> Requests for treatment or intermediate INDs/protocols or treatment IDEs follow a well-documented review process relevant to the medical product.

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- Patients reach a point in their clinical care when there is no generally acceptable alternative treatment—either because they have exhausted all available approved therapies and/or they are not candidates for open clinical trials.
  - Patients or caregivers typically search for available treatment options through a physician, but they may also initiate the research themselves, most commonly through online resources. It is during this time that patients and physicians often learn about the EA program as a potential avenue.
    - Patients and caregivers will occasionally reach out to manufacturers to check if they have products that are available through EA, or to FDA to generally understand how to proceed.
    - Because of confidentiality constraints, FDA cannot give patients or physicians direct contact information for manufacturers with INDs and IDEs without specific approval; however, the Agency can provide general information on where to search (e.g., ClinicalTrials.gov, literature reviews).
    - Manufacturers provide information about their EA policy through various sources and may answer physician or patient questions.
  - Physicians typically work with their health system (if applicable) and an IRB to understand any local requirements. At this point, patients and physicians typically contact payers to understand coverage options (e.g., for the treatment itself or any aftereffects).

## **Step 2: Application**

- If a potentially appropriate product has been identified and the physician believes the patient is a good candidate, the physician can present the treatment option to the patient and outline the potential risks and benefits associated with the product to support informed consent.
- For drugs and biologics, should the patient decide to proceed, the physician asks the manufacturer for access to the medical product and a letter of authorization to cross-reference the existing IND (if a separate IND submission is needed). If the manufacturer agrees to provide the medical product, the physician prepares the application for submission to FDA. For devices, if there is an IDE for the device, the FDA application process is led by the investigational device sponsor, and is submitted as a supplement to the IDE. If there is not an IDE, a physician can submit the required documentation.
- The physician must notify an IRB about the pending EA request, which is typically done in parallel to the FDA application. IRB approval is required before treatment unless it is an emergency application,<sup>37</sup> in which case the physician only needs to notify the IRB within five days following treatment. Health system policies vary regarding IRB review for EA; for example, some require IRB approval before emergency use.

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<sup>37</sup> For devices with no IDE, concurrence from the IRB chair and compliance with institutional policies is expected before treatment, but there are no specific regulations and it is understood that this may be a time-sensitive situation.

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- With the agreement of the manufacturer and in parallel with IRB review, the physician submits the completed application to FDA.
    - For drugs and biologics, applicants can use Form 1571 and 1572, which are used for all IND applications. Alternatively, physician sponsors can use Form 3926 for single patient requests. Form 3926 is an abbreviated form released in 2017 that streamlines the application to an estimated 45-minute completion time. Typically, sponsors need to submit the patient’s clinical history, rationale for the treatment with the investigational product, the proposed treatment plan (i.e., protocol), and the relevant patient protection measures (e.g., IRB concurrence/approval, informed consent documents, and institutional clearance, as required), and a copy of their curriculum vitae (CV).
    - For devices, applicants need to provide similar information, as well as an independent assessment from an uninvolved physician that the EA request is appropriate, though no specific form is required.
  - FDA evaluates the application and determines whether to authorize or deny the request. As part of the review, the Agency will collaborate with the coordinating physician to update documentation and refine the protocol, as needed.

### **Step 3: Treatment**

- If FDA authorizes the request, FDA documents the decision internally and notifies the physician of the authorization, and explains follow-up requirements.
- The physician communicates that decision to the manufacturer to initiate shipment of the investigational product.
- If the investigational product needs to be imported into the US for use, the manufacturer must ensure proper labeling and documentation for the product to pass U.S. Customs and Border Protection (CBP) inspection.
- The physician obtains and documents informed consent from the patient.
- The physician then treats the patient per the approved protocol. The payer may reimburse costs related to the treatment, which is determined on a case-by-case basis. In most cases, the manufacturer provides the unapproved medical product free-of-charge, though it is permitted to charge reasonable costs consistent with the conditions of the EA process used.

### **Step 4: Follow up**

- During the follow-up step, the physician documents the treatment outcome and adverse events, as needed or required by the authorized protocol.
- The physician notifies the relevant parties (e.g., FDA, manufacturer, IRB) about treatment status, as appropriate. Adverse events typically must be reported to FDA and the IRB at intervals specified by regulations and policy.
- The patient continues to receive treatment per the protocol until the treatment has been completed or is withdrawn.



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- For drugs and biologics, the physician must submit annual reports for as long as the IND is open, and is required to submit a follow-up report before the IND can be withdrawn or closed.
  - For devices, a follow-up report with the patient outcome and IRB approval documentation, if not previously submitted, is expected within 45 days of using the device. If EA is approved under an open IDE, safety information is also submitted as part of the IDE annual report.
  - If the payer grants coverage for the treatment, they generally decide whether to continue to pay for the associated care.

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## Glossary

AAN	American Academy of Neurology
ASCO	American Society of Clinical Oncology
CBER	Center for Biologics Evaluation and Research
CBP	U.S. Customs and Border Protection
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CME	Continuing medical education
CMS	Centers for Medicare & Medicaid Services
CTO	Chief Technology Officer
CV	Curriculum vitae
DDI	Division of Drug Information
EA	Expanded Access
EACC	Expanded Access Coordinating Committee
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
FFDCA	Federal Food, Drug, and Cosmetic Act
GAO	Government Accountability Office
HHS	U.S. Department of Health and Human Services
IDE	Investigational device exemption
IDSA	Infectious Diseases Society of America
IND	Investigational new drug application
IRB	Institutional Review Board
IDS	Infectious Diseases Society of America
MAPP	Manual of Policies and Procedures
NIH	National Institutes of Health

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OC	Office of the Commissioner
OHCA	Office of Health and Constituent Affairs
SOPP	Standard Operating Policy and Procedure
US	United States of America
VHA	Veterans Health Administration