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How Often Are Drugs Made Available Under the Food and Drug Administration's Expanded Access Process Approved?

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Abstract

In this review of individual patient expanded-access requests to the Center for Drug Evaluation and Research for the period Fiscal Year 2010 to Fiscal Year 2014, we evaluated the number of applications received and the number allowed to proceed. We also evaluated whether drugs and certain biologics obtained under expanded access went on to be approved by the Food and Drug Administration. Finally, we considered concerns that adverse events occurring during expanded access might place sponsors at risk for legal liability. Overall, 98% of individual patient expanded-access requests were allowed to proceed. During the study period, among drugs without a previous approval for any indication or dosage form, 24% of unique drugs (ie, multiple applications for access to the same drug were considered to relate to 1 unique drug), and 20% of expanded-access applications received marketing approval by 1 year after initial submission; 43% and 33%, respectively, were approved by 5 years after initial submission. A search of 3 legal databases and a database of news articles did not appear to identify any product liability cases arising from the use of a product in expanded access. Our analyses seek to give physicians and patients a realistic perspective on the likelihood of a drug's approval as well as certain information regarding the product liability risks for commercial sponsors when providing expanded access to investigational drugs. The US Food and Drug Administration (FDA)'s expanded-access program maintains a careful balance between authorizing patient access to potentially beneficial drugs and protecting them from drugs that may have unknown risks. At the same time, the agency wishes to maintain the integrity of the clinical trials process, ultimately the best way to get safe and effective drugs to patients.

Keywords

expanded access, compassionate use, US Food and Drug Administration

A core mission of the FDA is the premarket assessment of the safety and effectiveness of investigational new drugs and biological products (referred to collectively as "drugs" in this paper). However, the FDA understands that patients, particularly those with life-threatening diseases or conditions, may have an interest in obtaining access to drugs that have not yet been approved.

Wherever possible, the FDA believes enrollment in clinical trials remains the best option for patients who wish to gain access to investigational drugs. Clinical trial enrollment helps to provide adequate protection for patients and leads to the collection of data that may result in the approval of the investigational drug and, consequently, to wider availability. However, when patient enrollment in a clinical trial is not possible (eg, a patient is not eligible for any ongoing clinical trials, there are no ongoing clinical trials, or the patient does not live near an ongoing trial and cannot travel to participate), patients have the option to seek access to unapproved drugs if they have serious or life-threatening diseases or conditions and no comparable or satisfactory alternative treatment is available.

In 1987, the FDA formalized its expanded-access process, which facilitates access to investigational new drugs and biological products for patients with serious or immediately life-threatening diseases or conditions and who lack therapeutic alternatives. Expanded access can also be used to secure access to an approved drug where availability is limited by a risk evaluation and

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mitigation strategy and patients cannot obtain the drug under this strategy.

In expanded access, sometimes termed "compassionate use," the primary purpose is to treat a patient rather than to obtain data about the drug, as would be the case in a clinical trial. In operating the expanded-access process the FDA seeks to maintain a careful balance between facilitating patient access to potentially beneficial drugs and protecting these patients from drugs that may have unknown risks.

In August 2009, the FDA revised its expanded access regulations to increase awareness and knowledge about expanded-access processes and to streamline the procedures for obtaining investigational drugs for treatment use. Under those regulations, the FDA identified 3 categories of expanded-access investigational new drug (IND) applications[1–5] (In addition, the FDA accepts expanded-access protocols, which permit expanded access through reference to an existing, typically commercial, IND. These follow different procedures and are not considered in this analysis.):

1. Expanded access for individual patients (frequently referred to as "single patients") including for emergency use. Unless the FDA notifies the sponsor (typically the patient's requesting physician) that treatment may begin earlier, there is a 30-day period from the date that the FDA receives the application before treatment may begin. Under the regulations' emergency use provisions, treatment is typically initially requested and authorized by telephone (or other rapid means of communication such as email) and may start immediately on FDA authorization. The physician must agree to submit a written application within 15 working days of authorization.
2. Expanded access for intermediate-size patient populations. These are generally for more than an individual patient but for fewer patients than in the third category described below. FDA regulations do not have specific numerical limitations for when intermediate-size patient population expanded access may be appropriate. This determination generally depends on whether the drug is under development for marketing for the expanded access use and the number of patients with the disease or condition.
3. Expanded access for widespread treatment use. These are designed for use in larger patient populations and often bridge the gap between trial completion and potential approval while a marketing application is under review at the Agency.

This article focuses on the first category (individual patient expanded-access INDs).[2–5] For such applications, the FDA must determine that:

- The patient to be treated has a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- The potential patient benefit justifies the potential risks of the treatment use, and those potential risks are not unreasonable in the context of the disease or condition to be treated;
- Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded-access use or otherwise compromise the potential development of the expanded-access use; and
- The patient cannot obtain the investigational drug under another IND or protocol;

In addition, the patient's physician must determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition.

An important component of the expanded-access application process is a letter of authorization from the commercial sponsor of the investigational drug. The letter of authorization permits the FDA to refer to the commercial sponsor's application for information to satisfy submission requirements. The FDA has personnel who help requesting physicians to identify the appropriate FDA review division, locate contacts at companies, find company policies regarding expanded access, engage an Institutional Review Board, and determine whether there are ongoing clinical trials.[2–5] An FDA review of expanded-access requests includes knowledge of the totality of data and information that the commercial sponsor has submitted to the FDA for the development program, including data (eg, safety/toxicity data, dosing considerations) that may not be publicly available. The FDA does not provide clinical advice for the individual patient (this is the responsibility of the requesting physician), but the FDA can recommend revisions to the treating physician's desired treatment plan to better protect the patient's safety.[6]

The FDA acts quickly in response to individual patient expanded access requests and allows the vast majority of requests to proceed. For an emergency use application, access to the drug may begin on verbal authorization (usually over the telephone) by the reviewing FDA staff.[4] For nonemergencies, the FDA strives to respond promptly and has a median response time of 4 days. As noted above, if the FDA does not respond within 30 days, treatment may proceed.[6] (Certain expanded access protocols are not subject to

the 30-day requirement.) Although expanded-access submissions represent approximately one-third of all IND submissions, the vast majority of these are for individual patients and do not typically require substantial agency resources to review.

For this study, the FDA conducted a review of the expanded-access applications to the Center for Drug Evaluation and Research for the period Fiscal Year (FY) 2010-2014. We also evaluated whether drugs obtained under expanded access went on to be approved by the FDA. Finally, we considered concerns that adverse events occurring during expanded access might place sponsors at risk for legal liability.

Methods

A data set containing all expanded-access requests between FY 2010 and FY 2014 was obtained from the Center for Drug Evaluation and Research. This database included all individual patient, intermediate-size, and treatment use expanded-access INDs and protocols (6054 unique entries) and included both drugs and biologic products regulated by the Center for Drug Evaluation and Research. This project focused only on individual patient INDs, including individual patient INDs for emergency use, and thus excluded intermediate-size and treatment INDs and all protocols submitted to existing INDs.

The first step in cleaning this data set involved the removal of nonsubmitted INDs and duplicates. Nonsubmitted INDs included submissions in which an IND number was issued in error, submissions that were withdrawn by the sponsor, submissions where drug development under the IND had been suspended, or those where an IND number had been preassigned but no supporting documents had been received. We also removed 14 entries that were listed as both individual patient and emergency INDs. Exclusion of these entries, in combination with the removal of intermediate and treatment INDs and all protocols, resulted in a final data set with 5394 unique entries.

We next sought to standardize drug names for each remaining IND, as multiple drug names were present in the IND submissions—sponsoring physicians may have submitted expanded-access INDs for drugs identified by their commercial names in the United States or abroad, commercial veterinary names, code names of drugs used by the sponsors in investigational studies, or the chemical names of the active ingredient(s). A master drug list was therefore derived using the following 2-step process:

1. The provided drug name was entered into the Drugs@FDA search engine (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), which provides labels and other pertinent information on previously approved prescription drugs, over-the-counter drugs, and therapeutic biological products. If the drug was found, the initial drug approval date was abstracted and added to the drug master list. To be considered approved for this study, drugs had to be approved by September 30, 2015.
2. If the drug was not found, a simple search was conducted using Google, PubMed (http://www.ncbi.nlm.nih.gov/pubmed), and/or the National Cancer Institute's NCI Drug Dictionary (http://www.cancer.gov/publications/dictionaries/cancer-drug) to assess potential misspellings and similar errors. Alternative drug names found via this step were then entered in the Drugs@FDA search engine, as above. If the drug was not found after this step, the drug's potential commercial drug name, active ingredient, or drug code name (in that order) was added to the master list, and the drug was listed as not having been approved by September 30, 2015.

We calculated the numbers of INDs allowed to proceed and those not allowed to proceed. Additional analyses conducted focused only on INDs that were allowed to proceed, using both the individual IND and the unique drug (in this analysis, multiple applications for access to the same drug were considered to relate to a single unique drug) as the unit of analysis. Drug names are not presented in this document because of confidentiality protections associated with information about unapproved products, but aggregate data are presented by review division.

We produced Kaplan-Meier-style curves that described what percentage of INDs and unique drugs went on to be approved for any indication at various time junctures. For these analyses we included only drugs that had not been approved in any dosage form or for any indication at the time of the initial expanded-access application. For fixed-combination drugs, the drug was considered unapproved if at least 1 of the drugs in the combination had not yet been approved. All analyses were conducted using Microsoft Excel 2010 and SAS version 9.4.

To identify instances in which a tort allegedly arose in the context of expanded access, we searched WestlawNext, Google Scholar/Case Law and HeinOnline/Law Journals, not limited by date, using such terms as "tort liability," "product liability," "expanded access," "compassionate use," "investigational new drug," and "FDA." An analogous search for news articles using the same search terms was conducted using WestlawNext's news sources.

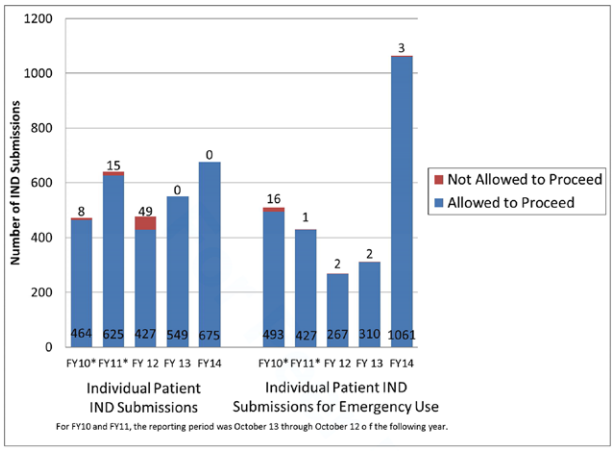

Figure 1. Individual patient expanded-access INDs, Fiscal Years 2010-2014. IND indicates investigational new drug.

Results

Analysis of FDA Expanded-Access Data

There were 5394 unique individual patient expanded-access IND applications during the study period, almost evenly split between individual patient INDs (n = 2812, 52%) and individual patient INDs for emergency use (n = 2582, 48%). Figure 1 presents these INDs by IND type. The average annual number of applications was 548 for individual patient and 512 for emergency use, with the highest number for each, 675 and 1061, respectively, occurring in FY 2014. During FY 2010-2014, the FDA authorized more than 98% of individual patient expanded-access requests received (99% and 97% allowed to proceed for emergency use and individual patient INDs, respectively). (These numbers are slightly different from what the FDA has presented elsewhere due to minor differences in methodology.)

Table 1 shows the top 10 FDA review divisions that received expanded access INDs, which together accounted for approximately 95% of individual patient expanded-access INDs; the remaining 12 divisions to which expanded access requests were submitted accounted for slightly less than 5% of applications. The majority of INDs were submitted to divisions that focus on infectious diseases (45%) and on oncology/hematology (37%). Table 2 presents the review divisions of the 10 most requested drugs during the study period. Together these 10 drugs accounted for almost 60% of all INDs submitted.

Overall, 3365 of the 5298 INDs allowed to proceed (64%) requested drugs that were approved for any indication by September 30, 2015. Figure 2 displays approval rates for INDs requested by application year and IND type. In each year except FY 14, approval rates were higher for individual patient INDs than for individual patient INDs for emergency use (range 46% to 71% for individual patient INDs and 46% to 83% for emergency-use INDs).

There were 408 unique drugs or unique fixed-combination drugs requested between FY 2010 and FY 2014. Table 3 shows that, overall, more unique drugs were requested using individual patient INDs than individual patient INDs for emergency use (305 and 182, respectively), whereas Figure 3 shows somewhat higher approval rates for drugs requested under individual patient INDs for emergency (range 36% to 48%) than for individual patient INDs for every year (range 32% to 40%). Overall, 30% (122/408) of all unique drugs for which expanded access was sought had been approved by September 30, 2015, including 39% of those originating in FY 2010 and 30% of those originating in FY 2014.

Figures 4 and 5 show the rate of approval over time, measured as the time since the first expanded-

Table 1. Top 10 Divisions to Which Individual Patient Expanded-Access INDs That Were Allowed to Proceed Were Submitted, FY 2010-2014

Rank	Review Division	Number	Percentage
1	Antiviral products	1226	23
2	Anti-infective products	997	19
3	Hematology products	885	17
4	Oncology products 1	848	16
5	Gastroenterology and inborn errors products	434	8
6	Oncology products 2	223	4
7	Gastroenterology products	175	3
8	Special pathogen and transplant products	143	3
9	Transplant and ophthalmology products	128	2
10	Neurology products	103	2
	Other divisions	136	3
	Total	**5298**	**100**

Oncology products 1 include Division of Oncology Products 1 (DOP1) and Division of Drug Oncology Products (DDOP). Oncology products 2 include Division of Oncology Products 2 (DOP2) and Division of Biologic Oncology Products (DBOP), respectively, which were combined due to division restructuring and renaming during the study period. DBOP indicates biologic products; FY, fiscal year; IND, investigational new drug.

Table 2. Ten Most Requested Drugs Under Individual Patient Expanded-Access INDs That Were Allowed to Proceed, Presented by Review Division and Their Approval Status as of September 30, 2015, FY 2010-2014*

Rank	Review Division (Number of INDs)[a]	Number of Requests	Percentage of Requests	Approved for Any Indication?
1	Anti-infective products (727) Special pathogen and transplant products (81) Transplant and ophthalmology products (54)	869	16.4	Yes
2	Antiviral products (573)	573	10.8	No
3	Hematology products (437)	442	8.3	Yes
4	Gastroenterology and inborn errors products (232) Gastroenterology products (71)	304	5.7	No
5	Antiviral products (235)	235	4.4	No
6	Gastroenterology and inborn errors products (119) Gastroenterology products (54)	173	3.3	Yes
7	Drug oncology products (98) Oncology products 1 (36) Oncology products 2 (14)	156	2.9	Yes
8	Hematology products (94) Oncology products (50)	153	2.8	Yes
9	Transplant and ophthalmology products (24) Anti-infective products (89) Special pathogen and transplant products (21)	134	2.5	No
10	Antiviral products (120)	120	2.3	Yes

IND indicates investigational new drug.
[a]Includes only divisions with more than 10 requests.

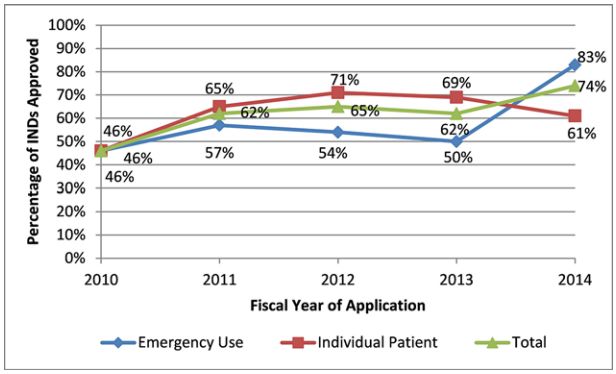

Figure 2. Percentages of expanded-access INDs that were allowed to proceed for which the investigational drugs were approved for any indication by September 30, 2015, by IND type and application year, FY 2010-2014 (n = 5298). FY indicates fiscal year; IND, investigational new drug.

access application rather than by cohort year, for those INDs associated with drugs without a previous approval for any indication or dosage form. Figure 4 shows that 20% of INDs were for drugs that were approved within 1 year after the initial expanded access IND was submitted and that 33% were approved by 5 years after the initial submission. Figure 5 presents the same data by unique drug and shows that almost one-quarter of drugs requested under individual patient expanded-access INDs (including those for emergency use) received marketing approval by 1 year after the initial expanded-access IND was submitted, and 43% received approval by 5 years.

Table 3. Number of Unique Drug Expanded-Access Requests That Were Allowed to Proceed by IND Type and Year of Initial Request, FY 2010-2014

Emergency Use	2010	2011	2012	2013	2014	All Years[a]
Drug approved[b] by 9/30/15	29	28	25	27	26	74
Drug not approved by 9/30/15	35	31	31	35	46	108
Total	64	59	56	62	72	182
Individual patient						
Drug approved by 9/30/15	30	36	33	40	38	86
Drug not approved by 9/30/15	45	64	70	66	81	219
Total	75	100	103	106	119	305
All INDs[c]						
Drug approved by 9/30/15	49	50	49	56	49	122
Drug not approved by 9/30/15	78	91	93	94	114	286
Total	127	141	142	150	163	408

FY indicates fiscal year; IND, investigational new drug.
[a]"All Years" total does not always add up to the sum of individual years, as drugs could have been requested in multiple years.
[b]For any indication.
[c]"All INDs" total does not always add up to the sum of individual patient INDs and individual patient INDs for emergency use as unique drugs because drugs could have been requested under both.

Product Liability Information

A search of the 3 legal databases identified 58 items in WestlawNext, 18 items in Google Scholar, and 69 items in HeinOnline. On closer inspection, none of these represented product liability cases against pharmaceutical companies relating to personal injuries allegedly sustained while using drugs obtained under the expanded-access process. The search of Westlaw Next's news sources yielded no relevant articles.

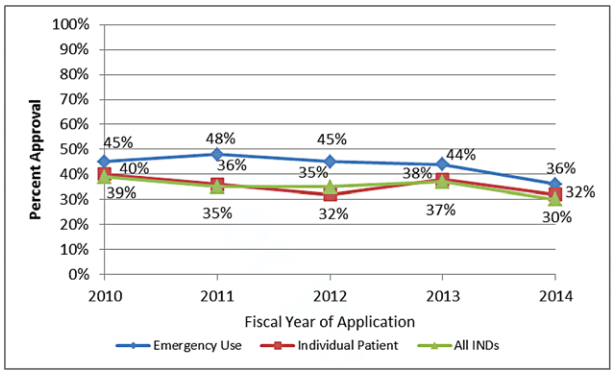

Figure 3. Percentage approval for any indication by September 30, 2015 of unique drugs for which expanded-access INDs were allowed to proceed by year of application, FY 2010-2014 (n = 408). FY indicates fiscal year; IND, investigational new drug.

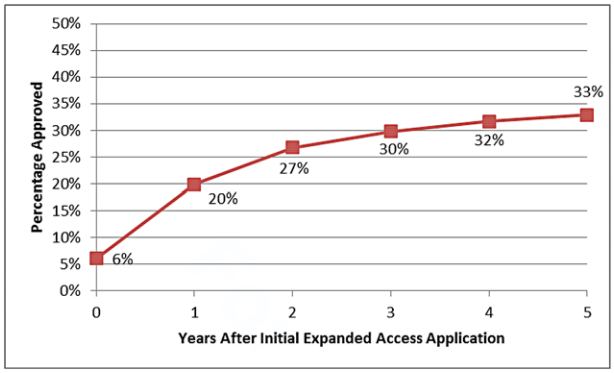

Figure 4. Percentage approval for any indication by September 30, 2015 for drugs for which expanded-access INDs were allowed to proceed, FY 2010-2014 (n = 2882). FY indicates fiscal year; IND, investigational new drug.

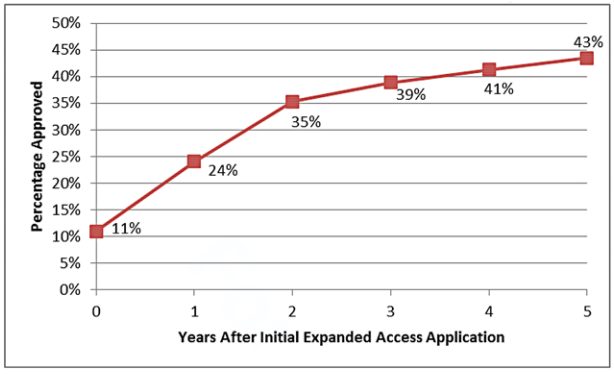

Figure 5. Percentage approval for any indication by September 30, 2015 for unique drugs for which expanded-access INDs were allowed to proceed, FY 2010-2014 (n = 471). FY indicates fiscal year; IND, investigational new drug.

Discussion

During FY 2010-2014, the FDA allowed more than 98% of the 5394 individual patient expanded-access requests received to proceed. As our analysis demonstrates, physicians and patients should not assume that these drugs will later be approved for marketing by FDA. During the study period, for drugs not previously approved in any dosage form or for any indication, 24% of unique drugs and 20% of INDs received marketing approval by 1 year after initial submission; 43% and 33%, respectively, were approved by 5 years after initial submission. Expanded access provides just that: access. There is no guarantee that the product sought will be effective and/or safe, much less that it will be effective and/or safe for the particular patient, and these individual INDs are not purposed to collect data on the drug.[7–10]

The FDA's consideration of an expanded-access application generally comes only after the commercial sponsor has agreed to provide the investigational drug. The FDA cannot require the commercial sponsor to provide its investigational drug for expanded access use. Sponsors may choose not to do so for various reasons, including lack of available drug, lack of adequate safety information, or a desire to focus their attention on completing the clinical trials necessary to support an FDA marketing application. There is some emerging evidence that individual companies have rejected more applications for a single drug than the FDA has rejected for all drugs over this entire study period. For example, 1 company indicated that it had turned down 98 of 160 applications for a single drug in a 6-month period.[11] Another company turned down "hundreds" of applications for its drug over 2 years.[12] In contrast, in only 96 instances over the 5-year study period did the FDA not allow the expanded-access use to proceed.

Some have cited potential liability concerns as another reason companies may not provide expanded access to their drugs, but we did not identify information about product liability cases involving the use of a drug in an expanded-access program.

The FDA is also aware of concerns that adverse events occurring during expanded access could place a drug development program in jeopardy. In fact, the safety data from individual patient expanded access requests can be informative to the commercial sponsor and can contribute to the overall development program for the investigational drug. From a public health perspective, early identification of important adverse events is beneficial and is critical in the FDA's evaluation of a drug's benefit-risk profile. Moreover, the agency understands that patients who do not meet the entry criteria for clinical trials but are treated under expanded access might be at increased risk for serious adverse events because of their advanced disease, concomitant medications, and/or comorbidities. FDA reviewers of these adverse-event data understand the context in which the expanded-access use was permitted and evaluate any adverse event data obtained from an expanded-access submission within that context.[2]

A recent analysis by the FDA revealed that, over the last decade, spanning almost 11,000 expanded access requests, there were only 2 instances in which a clinical hold was placed on commercial drug development due to adverse events occurring under expanded access. In both instances the development of the drugs continued shortly after these issues were addressed and the holds were lifted.[13]

Recent FDA Efforts to Improve the Expanded Access Process

The FDA has undertaken several initiatives to streamline the process for physicians to request expanded access for individual patients. In response to feedback that the expanded-access application form was challenging for physicians to complete, in June 2016 the FDA finalized a streamlined form (Form FDA 3926) for individual patient expanded access that is estimated to take 45 minutes to complete and also reduces the number of required attachments from 7 to 1.[3] At the same time, the FDA revamped its website and finalized 3 guidances (1 on the new form, 1 on charging for investigational drugs under an IND, and a more general guidance clarifying various aspects of expanded access).[2,3,5] The agency also developed simple information sheets for patients and physicians. The FDA welcomes stakeholder input in our ongoing efforts to balance the potential benefits of expanded access to investigational drugs against their potential risks.

Conclusion

This analysis seeks to give physicians and patients a realistic perspective on the likelihood of a drug's approval as well as to provide certain information regarding the product liability risks for commercial sponsors in providing expanded access to investigational drugs. The FDA maintains a careful balance between permitting patients to obtain access to potentially beneficial drugs and protecting them from drugs that may have unknown risks. At the same time, the agency wishes to maintain the integrity of the clinical trials process, ultimately the best way to get safe and effective drugs to patients.

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Declaration of Conflicting Interests

Dr McKee, Dr Markon, Dr Chan-Tack, and Dr Lurie have no potential conflicts of interest related to this article.

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