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Impact of Expanded Access on FDA Regulatory Action and Product Labeling

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Abstract

Background: The purpose of this study is to address concerns that expanded access may negatively impact the ultimate regulatory action and product labeling for new drugs. *Methods:* We performed queries of FDA's Center for Drug Evaluation and Research (CDER) document tracking system to determine the effect of expanded access on FDA's regulatory decision making from 2010 through 2016. We also examined product labeling to determine whether safety events occurring under expanded access had an adverse effect on the approved product labeling. *Results:* There were 321 regulatory decisions made by FDA, with 28% of the drugs having prior expanded access. The approval rate for drugs with expanded access (84%) was higher than those that did not (76%). None of the negative regulatory marketing decisions were based on the adverse experiences reported under expanded access. The vast majority of deaths and serious adverse events that occurred under expanded access were not interpreted by FDA to be due to the investigational drug and did not affect product labeling. There was only 1 instance, a drug-drug interaction, for which safety events occurring during expanded access alone lead to potentially adverse product labeling. *Conclusions:* There was no instance in which expanded access lead to a negative regulatory decision regarding a drug application, and there was only 1 instance that safety events under expanded access had a potentially negative effect on product labeling. Concern that expanded access will have a negative impact on drug development and review is not based on the evidence and is unwarranted.

Keywords

expanded access, new drug application, drug development, compassionate use

Introduction

The US Food and Drug Administration (FDA) has a long history of facilitating access to investigational drugs for the treatment of patients with serious or immediately life-threatening diseases or conditions that lack therapeutic alternatives. In our previous reviews of the Center for Drug Evaluation and Research (CDER) experience with expanded access, we have shown that more than 1000 applications are received each year, more than 99% of the individual access requests are allowed to proceed, the median review time is 4 days for nonemergency requests and less than 24 hours for emergency, and that FDA requests changes in 11% of those allowed to proceed to ensure patient safety.[1,2] Moreover, it is extremely rare for serious adverse events or deaths that occur under expanded access to interrupt the development program for an investigational drug.

Nevertheless, there continues to be residual concern amongst the pharmaceutical industry and legislators that FDA will use safety information obtained during expanded access experience to adversely affect drug development and review.[3] Prior analyses focused on the potential impact on drug development of adverse experiences under expanded access and this analysis focuses on the potential effect on marketing approval and labeling.[1,2] To address this concern, we reviewed all of the regulatory decisions, both negative and positive, and subsequent product labeling for those products approved by the Office of New Drugs (OND) in CDER since implementation of the Prescription Drug User Fee Act IV (PDUFA IV).

Materials and Methods

We performed searches of CDER's document archiving, reporting, and regulatory tracking system (DARRTS) covering the 6-year period of January 2010 through December 2016 to identify all of the new drug and biologic licensing applications (NDA and BLA) regulatory decisions by OND and whether there were any expanded access referencing those investigational drugs prior to the regulatory decisions. DARRTS is the informatics system that CDER currently uses to track activities, including medical officer reviews, related to the applications, reports,

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Table 1. Types of Expanded Access INDs and Protocols Referencing Investigational Drugs for Submitted NDA and BLA.

Type of Protocol	Number
Intermediate size IND	40
Intermediate size protocol	3
Single patient, emergency IND	345
Single patient, nonemergency IND	549
Treatment IND	4
Treatment protocol	3

Abbreviations: BLA, biologic licensing application; IND, investigational new drug; NDA, new drug application.

meetings, and documents submitted to the FDA for medical products regulated by CDER. New requests for expanded access are required to reference the commercial investigative new drug application (IND) or be a protocol in that IND.

The medical officer reviews were examined to determine whether safety information from expanded access experience was reviewed and how it was interpreted. In addition to the medical reviews, the labeling for approved products was examined to determine whether and how safety information from expanded access was incorporated into labeling.

Although there was no formal prespecified hypothesis to be tested and mostly descriptive statistics were performed, we did compare the rate of approval of drugs that did versus those that did not have expanded access experience prior to regulatory review using chi-square analysis by SAS (JMP version 12.1).

Results

During the 6-year period, there were 322 regulatory actions taken by OND on 261 molecular entities. Fifty-three (20%) molecular entities were biologics and 208 (80%) were small molecules. The potential regulatory actions included refuse to file, complete response, and approval, the former 2 being negative regulatory actions. The potential reasons for a negative regulatory action included lack of efficacy, unacceptable risk, inadequate quality or manufacturing, administrative issues, data integrity, and other.

The investigational drug had been used under expanded access prior to submission for 91 (28%) of the 321 NDAs and BLAs. The total number of expanded access INDs or protocols was 944. The breakdown of type of expanded access is shown in Table 1. For those applications that had prior expanded access experience, the median number of expanded access INDs/protocols was 4, with a range of 1 to 186. Although the number of treatment and intermediate-size INDs was lower, the number of patients treated in each was higher.

We examined whether having had expanded access experience prior to submission of an application had an adverse effect on the subsequent regulatory action. The likelihood of having a positive regulatory action (approval) versus a negative one (refuse to file or complete response) was greater for those applications that had expanded access (Table 2).

Table 2. Comparison of the Regulatory Actions for Applications That Did and Did Not Have Prior Expanded Access Experience.[a]

Regulatory Action	No Expanded Access, n (%)	Expanded Access, n (%)
Approved	175 (76)	76 (84)
Refuse to file	9 (4)	9 (10)
Complete response	47 (20)	6 (7)

[a]Nominal $P = .001$.

There were 15 negative actions (9 refuse to file and 6 complete responses) for applications that had prior expanded access experience. Examination of the medical reviews did not reveal expanded access experience as responsible for any of these negative outcomes. In contrast, one of the 76 approvals, uridine triacetate, was based solely on experience within expanded access (60 single-patient INDs and 1 treatment protocol).

The medical officer reviews and product labeling was reviewed for the 75 other approvals to determine what, if any, effect there was of expanded access on product labeling. Serious adverse events and deaths were described in the safety section of the medical reviews from the expanded access experience for only 12 (16%) of these remaining 75 applications. The vast majority of these safety events were interpreted to be due to patient comorbidities or their underlying disease. The safety events described included death, arterial ischemic events, myocardial infarction, hepatic failure, secondary malignancy, and nonalcoholic steatohepatitis. There were other events (eg, anaphylactoid reaction) that were observed in both expanded access and clinical trial experience and were included in labeling. A drug being developed to treat Cushing disease had an index patient with elevated liver function tests meeting Hy's law[4] criteria during expanded access. Further review of the investigational experience uncovered 3 additional Hy's law events in healthy volunteers previously treated. This risk was included as a Warning and Precaution in product labeling. There was only 1 drug, an antiviral, for which an adverse event was found in expanded access experience only and was interpreted to be due to the drug. A drug-drug interaction with amiodarone was observed under expanded access and not during clinical trial development. This drug interaction was included in product labeling.

Discussion

CDER receives over 1000 requests for expanded access to investigational drugs each year. The vast majority of these requests are for new single-patient INDs for emergency or nonemergency access to treatment.[1] FDA recognizes that expanded access to investigational drugs can play an important role in the treatment of patients with serious or life-threatening diseases or conditions. While FDA supports patient access to investigational drugs, enrollment in clinical trials is the preferred option for eligible patients wishing to gain access to investigational drugs. Clinical trials ensure adequate patient protection and are the best mechanism to provide evidence of

a drug's effectiveness and safety to support marketing approval. Therefore, expanded access may not be appropriate when there are actively enrolling trials for which the patient is eligible and can participate or if there are adequate available therapies for their disease or condition. Extremely rarely, as seen in this review, expanded access experience may serve as the evidentiary basis for effectiveness and/or safety for the approval of a new drug. In this way, expanded access may be an asset rather than a detriment to new drug development.

In contrast to a widespread belief, serious adverse events occurring during expanded access did not have a deleterious effect on drug development. We could not identify a single instance where safety findings under expanded access lead to an adverse regulatory decision, refuse to file, or complete response. In contrast, the applications for investigative drugs that had prior expanded access use (86%) were more likely to be approved than those that did not (76%). This, however, does not mean that expanded access is causative of a positive regulatory outcome. It may also be that drugs that treat serious or life-threatening diseases, a prerequisite condition for expanded access, are more likely to be approved.

Finally, we find little evidence that expanded access experience has a negative effect on product labeling when a drug is approved. There were only 2 instances in which safety data from expanded access was used to inform product labeling independent from clinical trial experience and one of those was positively. The majority of deaths and serious adverse events that occurred under expanded access were interpreted by FDA in the context in which they occurred, as required by regulation (21 CFR 312.32),[5] and did not affect either the regulatory approval decisions or product labeling. Patients treated under expanded access often have terminal illnesses and significant medical comorbidities, making interpretation of safety events and attribution to the investigational drug difficult. FDA does not attribute causality of safety events to the investigational drug as a default. There has to be a reasonable possibility that the drug caused the event, meaning that there is evidence to suggest a causal relationship between the drug and the adverse event.[6] The vast majority of safety events occurring under expanded access were either not thought to be due to the drug or similar events occurred during clinical trial experience and, therefore, were going to be included in product labeling anyway. There was only 1 instance in which a safety event occurring under expanded access only was included in product labeling. Whether or not uncovering a drug-drug interaction under expanded access can be thought of as a negative sequela is up for debate but we counted it as such. Nevertheless, to ignore such information and not include it in product labeling could put future patients at risk.

Although there are many legitimate reasons for companies to deny a patient expanded access to their investigational drugs,[7] fear that this experience will jeopardize clinical development or approval of a safe and effective drug for its intended use should not be one of them. In fact, expanded access experience may be used to support regulatory approval of a drug and provides some "real world" experience in the premarket space. This study demonstrates that FDA medical reviewers are skilled at discerning when serious adverse events are due to patient factors such as underlying disease, concomitant therapies, or comorbidities rather than the investigational drug. Concern that FDA will not interpret safety events occurring during expanded access in the context in which they occur is unwarranted based on the evidence.

Conclusions

The Center for Drug Evaluation and Research of the US Food and Drug Administration receives over 1000 requests for expanded access to investigational drugs each year. The vast majority are allowed to proceed in a timely manner. Over a recent 7-year period, there was no instance in which expanded access experience lead to a negative regulatory action for drug approval. There was only 1 occasion that a safety event during expanded access alone had what might be interpreted as a negative effect on product labeling. FDA recognizes that expanded access to investigational drugs is an important option for patients as long as it does not interfere with the clinical development of the investigational drug. FDA continues to play an important role in assuring the safety of patients receiving investigational drugs and interprets safety events in the context in which they occur.

Declaration of Conflicting Interests

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