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Ten-Year Experience for the Center for Drug Evaluation and Research, Part 2: FDA's Role in Ensuring Patient Safety

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Abstract

Background—The purpose of this study was to describe the role of the US Food and Drug Administration (FDA) in ensuring the safety of patients receiving investigational drugs under expanded access.

Methods—To better define FDA's role in the review of requests for expanded access, multiple queries of FDA's Center for Drug Evaluation and Research (CDER) document tracking system were performed. The queries identified reasons for, and outcomes of, expanded access requests for investigational drugs that were either not allowed to proceed or denied over a 10-year time period. An in-depth review of a random sample of single-patient, non-emergency investigational new drug (IND) applications that were allowed to proceed was also conducted.

Results—Overall, 99.3% of the applications for almost 9000 expanded access of an investigational drug were allowed to proceed. There were 62 requests that were either denied (38 emergency INDs) or not allowed to proceed (24 non-emergency INDs). The most common reasons for denying emergency INDs was that the patient was stable on current therapy and that it was not deemed an emergency. The most common reasons for not allowing non-emergency expanded access INDs to proceed were incomplete application, unsafe dosing, demonstrated lack of efficacy for intended use, availability of adequate alternative therapies, and inadequate information provided in the application on which to base a decision. A review of a random sample of 150 single-patient, non-emergency INDs revealed that FDA recommended changes to dosing, safety monitoring, or informed consent in 11%.

Conclusions—FDA plays a significant role in the protection of patients who receive investigational drugs under expanded access. An extremely small percentage of applications received are not allowed to proceed; however, FDA provides significant input based on information that may not be available to treating physicians in order to ensure patient safety under the applications that do proceed.

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Declaration of Conflicting Interests

No potential conflicts were declared.

Keywords

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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. We had previously reviewed the expanded access experience of the Center for Drug Evaluation and Research (CDER).[1] We observed that the number of expanded access applications received each year is increasing and that the FDA allows more than 99% of submitted applications to proceed. This extremely high rate of allowing expanded access investigational new drugs (INDs) to proceed suggested to some that the agency acts primarily as a “rubber stamp” and raised questions about the need for FDA review of these applications. To address this concern, the agency examined the decisions made and recommendations provided to IND sponsors during the review of expanded access applications.

Materials and Methods

We performed multiple queries of CDER’s document archiving, reporting, and regulatory tracking system (DARRTS) covering the 10-year period of January 2005 through December 2014. DARRTS is the informatics system that CDER currently uses to track activities related to the applications, reports, meetings, and documents submitted to the FDA for medical products regulated by CDER. New requests for expanded access to an investigational drug through an IND application require a review by FDA, and there is a 30-day period during which the drug may not be administered unless the IND sponsor is otherwise notified by FDA.

The first query was to identify all new expanded access INDs that were not allowed to proceed (ie, placed on clinical hold) during the initial 30-day safety review of the application. The purpose of this query was to determine the deficiencies that lead to a clinical hold and the ultimate outcome of the applications. Emergency requests for expanded use of an investigational drug are subject to denial because the request is made prior to official submission of an IND application. The practical result is equivalent to a clinical hold. We performed a second query over the same time period to identify those emergency INDs that were denied and the reasons for denial. Because it is possible for a sponsor to withdraw an application prior to it being placed on clinical hold, we performed a third query to identify all expanded access INDs that were withdrawn within 30 days of receipt. The purpose of this query was to determine whether initial interactions between FDA and the sponsor of the IND led to a withdrawal before the IND was placed on clinical hold. A final query was performed to generate a cohort of 150 randomly selected single-patient, non-emergency, expanded access IND applications submitted in the 2014 calendar year that were allowed to proceed to be reviewed individually. The INDs were selected in order of submission beginning on January 1 of that calendar year. The most recent year was chosen

to reflect current practice. This review was performed to determine the changes to the IND requested or required by FDA in order for those applications to proceed. For the final query, we excluded applications for investigational drugs for which FDA had provided a template application and/or consent form.

There was no formal statistical analysis plan for these queries; therefore, only descriptive statistics were performed.

Results

During the 10-year period from 2005 through 2014, there were 10,939 requests for expanded access for investigational drugs, of which 8922 were new IND applications to CDER. The remainder were protocols submitted to existing INDs. The types of expanded access requests were 115 intermediate-size population INDs; 4512 single-patient, non-emergency INDs (SPINDs); and 4295 emergency, single-patient INDs (eINDs). We determined that 24 of the 4627 new non-emergency expanded access IND applications received (0.52%) were placed on clinical hold, that is, not allowed to proceed. Six of the applications placed on clinical hold were for intermediate-size population INDs, and 18 were SPINDs. Thirty-eight of the 4295 eINDs (0.9%) were denied at the time of request, in other words, not allowed to proceed. Thus, the total number of expanded access requests submitted under new IND applications that were not allowed to proceed was 62 out of 8922 (0.69%).

For the 24 INDs placed on clinical hold, there was no further action for 8 of these IND applications, 6 were withdrawn, and 10 were eventually allowed to proceed. The average time until the clinical hold was released was 8.4 weeks, with a range of 1 to 22 weeks. The reasons and frequency for the INDs being placed on hold or denied are listed in Table 1. The most common reason for an SPIND being placed on hold was an incomplete application, most frequently lack of a letter of authorization from the commercial sponsor of the investigational drug. The most common reason for an eIND being denied was that it was not for treatment of an emergency. None of these 38 requests were to treat cancer or an infectious disease, and all of the patients for which documentation was available were reportedly stable on current therapies. It is not known how many of these requests were subsequently submitted as SPINDs. The large number of unknowns are a reflection of the process for emergency INDs, which are largely handled by telephone. Of the 8807 single-patient expanded access IND applications (SPINDs and eINDs) received during the 10-year period, 177 (2%) were withdrawn by the sponsor within 30 days of FDA receipt. Of these, 154 were IND applications that had been allowed to proceed and were withdrawn shortly thereafter, that is, within 30 days of initial receipt. The most common reasons for these withdrawals were that the patient had either completed their course of therapy or had died. Two were withdrawn by the sponsor for administrative reasons and 9 for indeterminate reasons. Ten patients either decided against going forward with the investigational drug or died shortly after submission of the request, and the applications were withdrawn before FDA took action. There were only 2 expanded access IND applications that were withdrawn by the sponsor within the first 30 days following the agency’s communication to the sponsor that the information submitted was insufficient to determine whether the treatment should proceed.

In 2014, CDER received 1492 expanded access IND applications, including 761 SPINDs. A sample of 150 SPINDs (20%) that were allowed to proceed were selected at random and reviewed in detail. This sample included applications submitted to 11 different review divisions, but the majority were for oncology and infectious disease indications. FDA requested or required 1 or more changes to 17 (11%) of these applications to protect human subjects before allowing treatment to proceed. These recommendations included a change in the dose or dose schedule (n = 11), enhanced safety monitoring of the patient (n = 8), and changes to the informed consent document (n = 11).

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 non-emergency access to treatment. 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 the patient's disease or condition. In addition, commercial sponsors may have valid reasons to deny access to an investigational drug (eg, limited supply).

FDA allows the vast majority of expanded access IND applications to proceed. In order for a patient to gain access to an investigational drug, the commercial sponsor must agree to supply the drug. The FDA cannot compel them to do so. If the sponsor of the expanded access IND is not the commercial sponsor, he or she must provide a letter from the commercial sponsor authorizing FDA to rely on the information contained in the commercial sponsor's IND (ie, product quality and toxicology) to support the expanded access application. We do not have information on the number of requests commercial sponsors receive each year, but we hypothesize that they may act as a filter, preventing applications that do not meet the criteria for expanded access from reaching the FDA. Of note, the percentage of intermediate-size population INDs placed on hold was higher than SPINDs: 6 of 115 (5%) versus 18 of 4512 (0.4%). The analysis was not designed to determine whether that difference is significant, however, it likely reflects the increased concerns regarding assurance of safety when larger numbers of patients are being exposed to an investigational drug.

FDA reviewing officials may authorize over the telephone the emergency use of an investigational drug for patients with an immediately life-threatening condition prior to written submission of an IND and institutional review board (IRB) review. The sponsor must agree to submit an IND application within 15 working days and report the use to the IRB within 5 working days. FDA does not normally place an emergency IND on hold because the request for emergency use of an investigational drug is made prior to submission of an application. These emergency requests, can be denied however if, in the view of FDA

reviewing official, the clinical situation does not warrant proceeding without submission of a written IND application and IRB oversight (eg, the patient does not have an immediately life-threatening disease or condition). The findings of this study suggest that this is a rare event. If the sponsor receives a denial, he or she is free to submit an application for a non-emergency, single-patient IND. Emergency-use applications are usually managed by telephone, email, or fax, and the documentation of these communications can be limited. Thus, we could not definitively determine whether the FDA recommended changes to the dosing, safety monitoring, or consenting of patients receiving treatment under emergency INDs.

One of the issues often raised is whether the FDA application process for expanded access is overly burdensome. Our analysis indirectly suggests that this process is not a major obstacle, at least for the applications that make it to the agency. Over a 10-year period, there were only 7 applications placed on hold for incomplete information, such as a missing letter of authorization, and only 1 of these 7 INDs was ultimately withdrawn by the applicant. Three were eventually allowed to proceed, and 3 submitted no further documentation. It was unclear in these instances whether the commercial sponsor had not been contacted or was contacted and refused to supply the drug. There were an additional 2 applications that were withdrawn after the applicant was informed that their application was incomplete. Thus, at most, 6 of the 8922 (0.07%) new expanded access IND applications did not go forward because the sponsor did not provide adequate information for the agency to reach a decision.

Another important finding of these analyses is that FDA provides significant input to ensure patient safety both for the applications that are denied and the INDs that are allowed to proceed. FDA reviewers may have confidential information from both commercial sponsors and other expanded access INDs that is not available to physicians who are requesting expanded access for investigational drugs. In addition, FDA review staff are informed about safety and efficacy profiles of other related investigational drugs in the same class. This has at times resulted in the agency recommending specific safety monitoring or concluding that the drug is not effective for the intended use, which may be different from that studied by the commercial sponsor.

FDA has also assisted sponsors by providing protocol templates for investigational drugs that are frequently requested under expanded access. Certain drugs used for specific indications have a very high volume of requests, particularly if the drug is not being actively developed by a commercial sponsor. To ease the burden for both requesters and the FDA, review staff have in some cases provided template applications online for use by physicians intending to prescribe such drugs. For the IND applications of these drugs, one might categorize them as having substantial FDA input; however, we did not include them in our analyses.

These findings demonstrate that even though the percentage of expanded access requests granted is extremely high, FDA provides a valuable service for patient protection and does not act as a “rubber stamp.” FDA staff have access to extensive information about investigational drugs because of its unique position as drug regulator for the US. Patient

safety is ensured through the careful review of these applications with input from FDA for the applications not allowed to proceed and those allowed to proceed.

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 granted and allowed to proceed. Over a 10-year period, only 24 applications were placed on clinical hold, of which almost half were eventually allowed to proceed. An additional 2 applications were withdrawn based on feedback from the FDA. A review of a random sample of single-patient, non-emergency INDs received in 2014 revealed that FDA required changes in dosing, safety monitoring, or the informed consent document to protect patient safety in 11% before allowing them to proceed. 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 ensuring the safety of patients receiving investigational drugs.

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References

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Table 1

Reasons for Clinical Hold or Denial of Expanded Access INDs From 2005–2014.

Reason	Clinical Hold, n	Denial, n
Incomplete application	7	
Unsafe dosing	4	
Lack of any demonstrated efficacy	4	
Availability of adequate alternative therapies	3	
Commercial IND on hold	2	
Product quality issues	2	
Inadequate safety monitoring	1	
Unreasonable risk	1	
Not an emergency		21
Duplicate requests		2
Unknown[a]		15
Total	24	38

All investigational new drugs (INDs) are subject to clinical hold, and only emergency IND requests for expanded access are subject to denial.

[a]The absence of any documentation prohibited determination of reason for denial.