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The Four A's of Expanding Patient Access to Life-Saving Treatments and the Regulatory Implications

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Summary

Individual patient expanded access is a process by which patients can obtain investigational drugs that have not been approved by the Food and Drug Administration (FDA) outside of a clinical trial setting from biopharmaceutical companies when no other alternative therapy is available. Currently, no industry-wide structural principles exist to help companies navigate this process while balancing the needs of getting a drug to the market as quickly as possible with providing potentially life-saving treatment to individual patients.

The Engelberg Center convened a stakeholder group to identify common themes and identify common principles related to expanded access, as none currently exist. The result was 4 A's - Anticipation, Accessibility, Accountability, and Analysis – to help assist patients, providers, and companies with expanded access. Process and capacity building recommendations for the FDA also were proposed to assist companies with sustaining expanded access programs.

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Introduction

Individual patient expanded access, sometimes termed “compassionate use,” refers to situations where access to a drug still in the development process is granted to patients on a case-by-case basis outside of a clinical trial, prior to completion of mandated clinical trials and approval by the Food and Drug Administration (FDA). This typically involves filing a single patient or emergency investigational new drug (IND) request with the Food and Drug Administration and voluntary release of the drug by the manufacturer. Generally, the following criteria must be met: there is reasonable expectation of meaningful benefit despite the absence of definitive clinical trial data, the patient has a serious or life-threatening condition, there are no comparable or satisfactory treatment alternatives, and there are no suitable clinical trials for the drug available to the patient. This form of expanded access, which is the focus of this paper, is different from the situation in which a drug is discharged to a large group of needy patients in the interval between successful phase 3 trials and presumed FDA approval, a strategy often termed a “treatment” IND or protocol, which was initially used in the 1980s for releasing zidovudine to patients with acquired immune deficiency syndrome.

A Call to Action: The Importance of Expanded Access Programs

The Engelberg Center for Health Care Reform at The Brookings Institution recently invited senior leaders from several pharmaceutical companies, two bioethicists, a senior FDA representative, and a patient advocate to share experiences and discuss organizational strategies related to expanded access (see acknowledgements). A driving factor for this meeting was a recent flurry of highly public cases of desperate patients seeking access to experimental drugs, which lead to social media campaigns and media coverage. Such cases included 7-year-old Josh Hardy (brincidofovir from Chimerix for disseminated adenovirus infection), 45-year-old Andrea Sloan (BMN673 from BioMarin for ovarian cancer), 41-year-old Nick Auden (pembrolizumab from Merck for melanoma), and 6-year-old Jack Fowler (intrathecal idursulfase from Shire for Hunter Syndrome). Expanded access requests to the FDA for new patients are increasing, from 1,000 patients nationwide in 2010 to more than 1,200 in 2012.¹ This

is likely an underestimate, since it does not include appeals made directly to companies.

In the wake of these events, it became clear that many biopharmaceutical companies had varying experiences and policies related to such access. From the domestic regulatory standpoint, the FDA revised its expanded access regulations in 2009, which define criteria that must be met to authorize expanded access, list requirements for expanded access submissions, describe safeguards that will protect patients, and preserve the ability to develop meaningful data about the use of the drug. Biopharmaceutical companies typically face a complex global environment in which legal and regulatory frameworks can differ substantially. At the meeting, a senior FDA representative indicated the agency has approved over 99 percent of expanded access requests submitted via single patient or emergency INDs since 2009, suggesting the regulatory agency is not a major barrier to expanded access. As such, provided the access request is reasonably related to the potential benefits of the drug, the biopharmaceutical company is almost solely responsible for the decision and liability regarding whether to grant expanded access to an individual. Still, the public belief persists that the FDA is the main bottleneck that restricts access. In April 2014, Representative Morgan Griffith (R-VA) proposed H.R. 4475, *The Compassionate Freedom of Choice Act of 2014*, designed to restrict the FDA’s ability to prevent the use of investigational drugs in terminally ill patients. Similarly, some states have passed “Right to Try” legislation to reduce FDA oversight, but contains no requirement that companies must make drugs available.²

The goal of our meeting was to identify common themes and possibly broad outlines to suggest industry-wide policies related to expanded access, as none currently exist. The group first discussed background issues related to expanded access and agreed on definitions. The meeting then focused on three topics. First, the group participants who play key roles in evaluating expanded access requests were invited to share narrative experiences in specific clinical cases, in an effort to lay the groundwork for trust and open discussion. Second, the group was asked to identify internal industry-specific structural

barriers, such as the existence of clear procedures or tracking mechanisms within companies to handle requests. Finally, the participants reflected on situations in which expanded access may not be appropriate, or where regulatory barriers or liability concerns may hinder expanded access. This paper reflects the authors' observations and assessment of the internal and external landscape, based upon information provided by the meeting participants.

Laying the Groundwork with Shared Experiences

The FDA allows companies to provide drugs and charge individual patients that do not meet the enrollment criteria for clinical trials geared towards regulatory approval through expanded access programs.³ These programs are meant to provide the drug directly to treat the patient's condition, rather than having the primary goal of collecting efficacy or detailed safety data in support of approval. Before 1987, the FDA lacked formal recognition of expanded access, although investigational drugs were provided informally.⁴ Since then, the FDA has instituted novel classes of individual INDs so that a company sponsor or licensed physician can legally obtain treatment access from the FDA to provide a drug while it is still in the approval process.⁵ Essentially, this provides companies a legal exception from the law to ship unapproved drugs across state lines, and if they desire, to charge for them. These INDs are designed solely for the potential benefit of desperate patients and not intended to formally collect safety or efficacy data that could potentially inform a regulatory decision, but can have regulatory impact, nonetheless.

At the outset, several participants objected to the term "compassionate use," since it introduces inherent value decisions, can emotionally charge discussions, and does not recognize that there may be valid and ethically appropriate reasons for denial. The generally agreed upon term "expanded access," is used throughout this paper. (One participant suggested the term "early access.") Ideally, the term would make it obvious that this is access to an unapproved drug, in order to temper expectations of favorable results. Somewhat confusingly, the FDA uses the terms "expanded access," "access," and "treatment use" interchangeably to refer to the use of a drug, and of which none clearly identify the stage of development.⁶

Participants shared numerous examples of requests for expanded access and explained that their companies handle anywhere from a handful to several hundred requests per year. The following selected stories illustrate the wide range of experiences and situations that companies encounter when navigating the complex decisions involved in administering an expanded access program. Several other examples were discussed and the specific participants expressed that they would be willing to share these particular examples publicly.

Chimerix, a 54-employee company based in Durham, North Carolina, is developing the drug brincidofovir and previously had created an intermediate expanded access protocol for the drug (CMX001-350) as encouraged by the FDA following over 200 emergency INDs granted for access to brincidofovir.⁷ One such case was for an armed services member with previously undiagnosed acute myelogenous leukemia who developed life-threatening vaccinia infection following smallpox vaccination in 2009.⁸ The patient received the drug from Chimerix through an emergency IND. After two years, the company had not secured FDA approval for the drug and eliminated expanded access in February 2012 in order to focus on studies which would inform a regulatory decision. In March 2014, Chimerix originally rejected an emergency IND request for 7-year old, Josh Hardy, who was critically ill from disseminated adenovirus infection after bone marrow transplantation. A highly public social media campaign targeted the company in the wake of this decision, and the experience was traumatizing for many of the employees. Following discussion with the FDA, Chimerix initiated a new clinical trial for the treatment of adenovirus infection in order to collect safety and efficacy data to support an NDA submission. Hardy was the first patient enrolled in the clinical trial, and his family reported through several media outlets that he recovered from the adenovirus infection and was discharged home.

One biopharmaceutical company representative described receiving a middle-of-the-night telephone call directly at home, with an emergent, time-sensitive request for an experimental therapy for a critically ill child with a rare acute disease in a foreign pediatric intensive care unit, where regulatory standards were different from those in the U.S. The ideal pediatric dosage was unknown, and only limited safety data and clinical details were available. Urgent efforts were made to gather more information and

the request was approved, but despite these efforts the patient did not survive.

Bristol-Myers Squibb began a clinical trial for a cancer drug several years ago.⁹ A woman with pancreatic cancer enrolled in the trial and saw that her tumor was no longer growing. After the 3.5 year trial, the study closed because the drug was deemed ineffective for all other patients and was not approved for further development. However, the company continued to provide the drug for the one woman for whom the drug was effective through a single patient IND for an additional 9 years.

To demonstrate the volume of expanded access requests, one participant showed several messages on his mobile device during the half-day discussion, directly from patients who had located his email addresses through on-line searches, to plead for expanded access to an anticancer therapy.

Development of Structural Principles: The Four A's

Broadly, no specific industry-wide consensus on expanded access procedures exists. As a result, there is significant variation in company policies and procedures. During this phase of discussion, participants shared their own company strategies and suggested possible areas of consensus that might form the basis for shared principles and industry-wide practices. These suggestions fell into four categories, which we termed **The 4 "A's"**: Anticipation, Accessibility, Accountability, and Analysis (see **Figure 1** on page 6).

1. Anticipation

First, the group agreed that large and small companies should anticipate the need for and creation of expanded access programs when developing drugs expected to generate expanded access requests and as part of the drug development plan. This is particularly important for drugs that might be considered for priority or breakthrough designation during FDA approval. In these cases, companies should strongly consider developing a written expanded use policy with clear guidelines for inclusion and exclusion, which would also feature a defined review process, clear decision making criteria, and a defined time frame for response to requests. This also allows companies to plan for the demands that may be placed on their supply chain and staff resources to ensure sufficient supply for

investigational and expanded use purposes. Identifying a decision maker within each company and for each disease area/product will also help patients or physicians reach the appropriate contact when requesting a drug, as well as assist the company in gaining expertise in responding to these requests. For example, one large company identifies one point of contact for all expanded access requests regarding each product and posts that individual's contact information on the website.

In the early stages of drug development, supplies of investigational drugs are extremely limited. This is often because the technically-challenging process of optimizing drug product manufacture takes a considerable amount of time. Low yielding manufacture batches are not uncommon at the early phases of research. Some companies do not approve expanded access requests because they do not have enough of the drug in stock to supply these external requests and meet the needs of investigational study patients and individuals participating in clinical trials, an issue which may be particularly acute for biologics. Smaller companies may have more resource constraints, such as inadequate staff to manage requests or supply chain and logistics issues. One representative suggested that if a company had early transparency from regulators about the final numbers of subjects they would be willing to accept to achieve drug development milestones, it would make it much easier for the company to feel less reservation about its drug supply. (It may be beneficial for companies to analyze their financial ability to provide drugs potentially at no cost or when there is not a large enough supply, ideally in a transparent manner.)

2. Accessibility

Once an expanded access policy is anticipated and developed, the second key principle the group identified was making the policy accessible to all individuals who may qualify. First, for patients, with guidance from their treating physician, the company making the drug should always steer the patient to enter a clinical trial (if they meet eligibility criteria). If the contacted company cannot accommodate the patient, they should steer them to other open trials if possible, even if sponsored by another company. Many of our participants noted that this already occurs.

The group was particularly cognizant of the disparity in access to drug companies and their expanded access programs: patients with savvy social media strategies are more likely to succeed in navigating across organizational constraints than without similar sophistication. The group believes that increased accessibility would assist in making opportunities for expanded access more equitable. In addition, these policies could help educate patients and physicians about submitting legitimate expanded access requests and help decrease the costs of reviewing inappropriate requests on the company (for example, if there are other proven therapies or the situation is not life threatening).

If the patient is ineligible for a trial, the patient should be able to easily access the written expanded access policy online. For example, both large and small companies like Pfizer, Bristol-Myers Squibb, Shire, and Merck post their expanded access policies on their websites, though the terminology may in some cases be complex. In addition, Janssen has developed a video explaining their policies in non-technical terms. Ideally, such policies should be available in some web based or public facing platform to both patients and physicians and written in a clear manner that is jargon free and accessible to individuals at various education levels. Most participants felt strongly that requests for expanded access should originate from a medical provider, not from a patient, since expertise is needed to first screen appropriate candidates. This is consistent with current FDA regulations for an IND, in which a physician or qualified medical expert must sponsor an IND or serve as an investigator under an existing IND for expanded access.

3. Accountability

Third, companies should have accountability to the requesting party for expanded use requests that they receive and review them within a specified, transparent amount of time. If the request could not be approved, the company should consider clear communication and provide an explanation of why the request was turned down. In these cases, some participants suggested that the company might also consider instituting an appeals process by which a patient can receive an additional review if not approved, potentially from a non-binding third party such as an independent, multidisciplinary body or a regulatory agency like the FDA. (Two participants,

however, were uncomfortable with any third party review.)

Companies can track expanded access requests in order to guarantee that the patient has received follow-up and that the communication loop has been closed. One large pharmaceutical company conducted an internal audit of its expanded access procedures and found that the largest problem was that employees did not know where to find information. Another representative noted that it is important to maintain consistency across patients and the process of requesting a drug.

4. Analysis

The final principle would encourage companies to release timely analysis of data from expanded access patients. In addition to tracking communication, companies should keep a database of the number of requests and outcomes, in a manner that doesn't slow getting drugs to needy patients rapidly. One company refined its internal tracking tools to determine who was requesting drugs, for what conditions, and where they lived. Where possible, companies might be encouraged to share anecdotal or preliminary safety or efficacy data from expanded access in peer-reviewed or other refereed venues in a prudent time frame following collections, if this is available or known. This is not always possible, because emergency INDs do not require provision of safety or outcome data to the company.

There are several challenges associated with operationalizing this in the current model, namely the appropriateness of anecdotal data, the level of detailed safety and efficacy data currently available through expanded access, suitability for publication, and funding for these activities in the current budget climate. One potential approach to address this is funding from federal or state regulatory agencies or payers for the reasonable costs of follow-up and reporting outcomes.

Regulatory Considerations

The participants then discussed the types of risks, including regulatory and financial, that may affect companies' expanded access policies. When a company is considering expanded access requests, they consider the risks-benefits of providing the drug outside of a clinical trial as well as the potential for any regulatory issues in an era of litigation and an increased threshold for demonstration of safety.

FIGURE 1: The Four A's: Principles for Model Individual Patient Expanded Access Programs

PRINCIPLE	DEFINITION	EXAMPLES
<i>Anticipation</i>	Planning for expanded access requests (e.g., resources, staff, supply and policy)	<ul style="list-style-type: none"> • <i>Inclusion criteria for clinical trials (if known)</i> • <i>Supply chain logistics</i> • <i>Written expanded access policy</i> • <i>Specified decision maker to handle requests</i>
<i>Accessibility</i>	Transparent and easy to find contact information and expanded access policies for physicians and patients	<ul style="list-style-type: none"> • <i>Easy to access information online</i> • <i>Audience-specific information</i> • <i>Information about open clinical trials (even if outside company)</i>
<i>Accountability</i>	Defined response period for expanded access requests and appropriate closed-loop communications	<ul style="list-style-type: none"> • <i>Set timeframes for review of requests</i> • <i>Written or oral communication to physician re: request</i> • <i>Consider appeals process</i> • <i>Tracking of requests and process feedback</i>
<i>Analysis</i>	Collection, tracking and data review related to expanded access requests and outcomes	<ul style="list-style-type: none"> • <i>Data collection on number of requests, etc.</i> • <i>Reporting data (e.g. publication in reasonable time frame)</i>

While a company’s provision of a drug for expanded access is voluntary, the FDA does require the company to collect and report safety data. Notably, none of the representatives felt that the FDA is a major regulatory barrier to processing and approving expanded access requests once the sponsor has reviewed the request, assessed the benefit-risk, and determined the request meets FDA requirements and evidentiary standards. In addition, the attendees felt that adverse effects and related liability risk were not of particular concern given that the drugs are assessed on a risk-benefit analysis.

However, companies that make drugs in particularly limited markets with small numbers of patients (for example, for unusual diseases with less than 200,000 patients nationwide which may justify a special designation called “orphan status”) may be more concerned about restrictive labeling if an unusual adverse event occurred even in one or two patients during expanded access of an orphan or small market therapy. However, there is no data of which participants were aware and no public reports that an adverse event during expanded access has harmed regulatory approval.¹⁰ The group opinion was that that safety data would be available eventually in any event and an FDA “safe harbor” provision would not

necessarily affect companies’ willingness to accept more requests for expanded access. A final concern was that there is no regulatory mechanism to consider data from expanded access in the evidence generation process for approval.

An Expanded Role for the FDA: While the FDA may not serve as a strong barrier to expanded access, the group considered strategies to promote equitable and fair access. For example, some argued that the breakthrough or priority review categories for FDA review might identify products that could have high potential for expanded access requests. This designation expedites “the development and review of drugs for serious or life-threatening conditions.”¹¹ As of mid-April 2014, the FDA had received nearly 180 requests for breakthrough designation, with 44 requests granted.¹² By hastening the drug development process, the FDA has already begun to bring drugs that have a reasonable expectation of benefit to the market faster. In order to receive breakthrough therapy designation, current legislation might be amended so companies could be asked to provide evidence that the 4 A’s are being followed in some capacity.

The FDA might also assist companies in establishing expanded access programs during open clinical trials in two main areas: process and capacity building. First, in terms of process, the FDA could be asked to create a defined path for regulatory approval with provisions that would encourage companies, both large and small, to include plans for expanded access programs when developing a drug. While FDA's draft guidance related to INDs notes that larger expanded access programs could threaten enrollment in clinical trials,¹³ and some participants agreed that this was a significant issue, not all companies have had difficulties enrolling patients in both clinical trials and expanded access programs. For example, one large pharmaceutical company left a Phase 1 clinical trial open for a promising therapy while concurrently enrolling individuals who didn't qualify for open clinical trials into an expanded access program, without appreciable leakage of enrollees in their advanced phase trials that might affect the key development pathway.

Second, the FDA could support convening around capacity building and sharing best practices with companies. With the understanding that there are many small biotechnology or pharmaceutical companies with limited budgets and staff, the FDA could foster a partnership of large and small companies. This partnership could be achieved by convening meetings where companies share their experiences in creating and sustaining expanded access programs. This could be supported by creating a database for these shared ideas, as well as any expanded access data that can be made legally available, such as how many requests are granted or patient outcomes.

To ensure equitable, consistent, and transparent review of requests, some companies suggested the use of an impartial external advisory board. Similar to an unbiased review from an institutional review board (IRB), this committee could have an advisory or decision making function. Companies with supply constraints may feel that if they cannot give the drug

to everyone who requests it, then they should give it to no one. This committee could help the company triage the patients who would benefit the most, and would be protected from liability.

Next Steps

The most efficient and equitable way to make new effective treatments to the largest number of needy patients is regulatory approval, accelerated or otherwise, following successful demonstration of efficacy and safety for a given indication in a specific population. Until that process is complete, access to an experimental therapy is by definition an additional risk, as the agreed necessary safety and efficacy have not yet been demonstrated. True informed consent in this setting is difficult to obtain (i.e. studies have shown that severely ill patients, such as those with life-threatening circumstances requesting expanded access, had less retention of information discussed in the informed-consent process and less-clear understanding of the risks of therapy compared to healthier patients¹⁴).

One position companies and regulators can consider is that the default answer to expanded access requests should be affirmative, unless there are compelling reasons for not approving requests to patients with life-threatening illnesses. (Such reasons, for example, might include limited treatment supply or lack of reasonable expectation of benefits versus risks.) Such a position would require, however, that there be broader industry, clinician, regulatory, and patient advocacy agreement of shared principles. This paper outlines the experiences, structural principles, and regulatory considerations of a small group, but further meetings may convene a broader group of stakeholders to build upon these concepts. Such consensus-based approaches might lead to durable systems that meet the needs of desperate patients who have run out of options—while allowing innovation to continue to benefit those who may come afterwards.

For more information about the Merkin Initiative on Payment Reform and Clinical Leadership or the Engelberg Center for Health Care Reform, visit www.brookings.edu/health.

For inquiries or interview requests regarding this issue brief, media may contact Michelle Shaljian at mshaljian@brookings.edu

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