Expanded Access
The Past, Present and Improvements for the Future

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Expanded access is a program that provides patients with investigational medicinal products (IMP) for treatment purposes. These patients are often excluded from clinical trials but could still benefit from access to the drugs, biologics or medical devices being tested. While, in concept, expanded access represents a way to help more patients receive new and developing treatments, in reality, the process is complex and often misunderstood.

This white paper is intended for a wide audience, covering the history of expanded access, the range of regulatory, economic and logistical challenges involved and several considerations to help organizations design more effective programs.

Expanded Access: A History

Expanded access is often considered a new concept, but it has been around since the 1970s when patients excluded from clinical trials wanted access to new oncology and cardiovascular drugs. However, it was not until the 1980s, during the HIV/AIDS epidemic, that the Federal Food and Drug Administration (FDA) changed regulations. Prior to HIV/AIDS, most requests for expanded access were from single patients, however, in 1987, the FDA began allowing access to larger groups of patients outside clinical trials.

With the ubiquity of the internet in the early 2000s, patients and physicians easily found information about ongoing clinical trials. In 2013, a patient with ovarian cancer, Andrea Sloan, became a staunch patient advocate for expanded access. While her fight for access did not help her in time, it did lead to the 21st Century Cures Act, signed into law December 13, 2016. This act was designed to help accelerate medical product development, and to more quickly and efficiently provide patients with access to IMPs.

As a result of this act, every pharmaceutical and biotech company operating in the United States was required to have an expanded access policy, and companies were required to have clear patient communication indicating the length of the request process. However, as of March 2018, only 72 percent of companies have complied with this regulation.

Expanded Access: Criteria and Mechanisms

Four Criteria for Expanded Access

Expanded access is used as an umbrella term. It is also known as compassionate use, single patient investigational new drug (IND), emergency IND, named-patient use, special access scheme, special scheme and nominal trial. However, expanded access should not be referred to as pre-approval access because many expanded access requests are for IMPs never approved by the FDA.

For pharmaceutical and biotech companies, there are four criteria to meet in order to offer patients expanded access:

1. The patient must have no other effective treatment options demonstrating an unmet need.
2. Administering the IMP cannot do more harm to the patient than his/her disease state.
3. A company needs to have the ability to accept the expanded access request, for example, the availability of existing safety and efficacy data from Phases I-III.
4. Accepting an expanded access request cannot interfere with ongoing clinical trials.

In addition to understanding the criteria for expanded access, it is important to note what expanded access is not. For example, expanded access is not a clinical trial for research, but rather a way to provide treatment to patients with serious or life-threatening conditions disqualified from clinical trials who have no other treatment options. Expanded access is not a bridging study, nor a study conducted in the gap between clinical trial

FDA Criteria for Expanded Access

- The patient has a serious disease or condition, or their life is immediately threatened by their disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the IMP will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Understanding Expanded Access in the Real World

Criteria 2: Not causing more harm

A company received its first expanded access request from a single mother with stage 4 breast cancer. The new expanded access team was excited to help this patient. The company had the supplies to give this patient the IMP so the team took the request to the Global Expanded Access Committee (including C-level employees from medical, commercial, supply, legal and marketing) for approval at the company.

Three hours into the meeting the chief medical officer explained that this request could not be granted because the drug would do more harm to the patient than her disease, and make the patient's death more painful. Therefore, the company could not help the patient.

Understanding Expanded Access in the Real World

Criteria 4: Not interfering with ongoing trials

A company was testing a new oncology drug, and had access to a large patient population for its clinical trial. Around the time the company put in the submission for clinical trial approval, the expanded access team knew there would be several patient requests for expanded access. The IND required access to 24 weeks of treatment, and by the time the company set aside supplies for clinical trial patients, there were not enough supplies to grant expanded access requests. Despite initial excitement to supply this drug, the company was unable to offer expanded access to anyone outside of the clinical trial.

Phases I and II. While some small companies will use expanded access data to help supplement submission data, most large pharmaceutical companies do not. Using data from a patient excluded from the trial can change trial endpoints, and often excluded patients have comorbidities that could introduce confounding factors into a data set.

Expanded access is not a process to provide IMPs to patients who could not otherwise afford them, nor is it a way to increase facility affiliate sales. Expanded access is sometimes confused with continued access, which is giving a clinical trial patient access to an IMP after the clinical trial ends. To receive continued access, a patient must demonstrate that the loss of IMP access would cause him/her harm.

Mechanisms for Expanded Access

Requests for expanded access can come during any phase of a clinical trial. When a company publishes results of an ongoing study using new IMPs, it should expect increased expanded access requests. Companies can offer expanded access in two ways: one, to a single named patient, or two, to a group or cohort of patients.

In the first case of a single named patient, the patient's physician acts as a sponsor and makes a formal request for expanded access on the patient's behalf. Some companies prefer to only offer single patient expanded access because this mechanism is more flexible. If the patient meets expanded access criteria, the company often provides the IMP for free, however, per FDA guidelines companies are allowed to seek reimbursement for IMPs given through expanded access. Recipients can only be charged direct costs, such as manufacturing and shipping; companies are not allowed to charge market value. In the case of a special license sale, a company can charge full market value, but this is specifically for requests from countries where an IMP will not be marketed if it receives regulatory approval.

Companies can also offer expanded access to a cohort of patients, in turn becoming the sponsor. While this may look similar to a clinical trial, it does not require the same level of protocol. The only data companies are required to keep is on adverse events (AE) or serious adverse events (SAE). Companies only need to provide minimal support to cohort sites, and often know little about the cohort patients. The advantage of offering expanded access through a cohort is reducing the administrative burden for regulatory agencies, as well as physicians sponsoring single patients. The disadvantage of cohorts is the additional work for companies because cohorts require a protocol, a label that must be approved, as well as specific packaging.

Examining Expanded Access Challenges

Running an expanded access program is not straightforward. One of the biggest challenges for designing an expanded access program is not knowing how many or when patient requests will be made. This is why a formalized process and clear communication within a company is critical, because clear expectations help with program success. Expanded access programs need to have coordinated involvement from several departments within a company, such as medical, bioethics, legal, safety, quality, drug supply, finance, marketing, communications and project management. Often, the companies also need to coordinate with outside patient advocacy groups.

A company has to be prepared for unknown outside influences as well when designing its expanded access program. For example, with the advent of social media, patients can generate a lot of public attention with their expanded access requests. Josh Hardy was a 10-year-old patient who struggled with a rare cancer since birth and his physician requested expanded access to a drug being tested by Chimera. The company initially denied the request because it did not have capacity to fulfill it, but Hardy's family started a widespread social media campaign, #SaveJosh, and essentially forced Chimera to provide expanded access.

In addition to preparing for unknown factors, companies need to create an exit strategy. Before granting an expanded access request, a company has to consider how long a patient is likely to live and whether there will be enough supply. It is also critical to have a process in place for when the IMP is either approved or denied by the FDA.

Designing Your Program: Important Questions

- How long will a patient need expanded access to IMPs?
- In which markets are you planning to sell your IMP?
- When do you plan to submit your data?
- Are patients from other countries likely to request expanded access?
- If you charge a fee for expanded access, what is your pricing strategy?
- Will materials be set aside for expand access requests?
- What are your communication strategies for patient requests?
- Have you established clear communication among top level staff for your expanded access program?
- Is the patient request really an unmet medical need? Do you know if there are any similar competing drugs soon to be on the market?
- Do you have an exit strategy?
- Do you have the resources to respond to expanded access requests?

While a company can forecast the number of expanded access requests it may receive for an IMP, it has to be careful not to solicit use of or advertise for that IMP. Communication around any IMP needs to be carefully constructed to ensure patients do not believe an IMP is a known cure for any disease state.

Different countries, different regulations

Another challenge with expanded access is the nomenclature. Different countries use different terminology to describe expanded access, which can lead to confusion. All countries in the European Union (EU) allow ex-

panded access, however, each country uses slightly different terms and regulatory practices. A company needs to consider where it will provide expanded access to patients and stay up to date on those countries' regulations.

Another way countries differ aside from terminology is in mechanisms. Some countries only allow expanded access for named patients while other countries only allow cohorts; and each country has different requirements around how many patients are needed for a cohort. Materials and data collection can vary as well. Some countries allow clinical trial materials to be imported while other countries require commercial materials. Other countries require additional data collection beyond AE and SAE.

Expanded access can also be used as a way to continue delivering IMPs to patients that participated in the clinical trial but where the sponsor may not ever intend to file for approval in that country's market.

Politics within and between countries have been known to influence expanded access. For example, one company approved the request for a named Lebanese patient to receive expanded access for an IMP. The company had the necessary materials along with a label that identified multiple countries running the clinical trial. However, one of those countries was Israel, and the Lebanese government was offended by receiving products with Israel on the label. In the end, the company had to write a letter of apology to the Lebanese Minister of Health.

Many aspects must be considered for a successful expanded access program to avoid regulatory and financial burdens. More expanded access requests are denied than approved by companies because of the challenges involved and the complexities of arranging IMP supply.

The Future of Expanded Access

Right to Try

In May 2018, U.S. President Donald Trump signed the Right to Try Act bill into law. This act gives terminally ill patients the right to seek drug treatments that have passed Phase I clinical trials, but are not yet approved by the FDA. Right to Try laws already exist in 39 states, and it differs from the 21st Century Cures Act because it removes FDA approval from the expanded access request process. The purpose of removing the FDA is to allow patients access to IMPs more quickly.

Right to Try legislation first came to the congressional floor in August 2017. The discussions spanned a year because Congress was trying to establish a definition for who should have access to IMPs. Legislators also discussed, and included in the bill, incentives to doctors and hospitals in the form of legal protections unless "reckless or willful misconduct" or "gross negligence" can be proven. However, Right to Try raises several concerns. Only 10 percent of IMPs that pass Phase I clinical trials are deemed safe and effective, and nearly 70 percent of expanded access requests are for IMPs that never receive FDA approval.

One can argue there is little difference in the Right to Try Act and the FDA's expanded access program. Many of the regulations in the bill are processes the FDA already put in place. This bill only removes FDA approval, and promotes IMPs that may not be safe for patients given that one of the criteria for expanded access is the IMP cannot be more harmful than the disease.

Right to Try is based on several assumptions of the expanded access process that do not align with reality, as described in the table below.

Misperceptions & Assumptions of Expanded Access	Examining the Realities of Expanded Access
The FDA is a bottleneck in expanded access request approval.	The FDA approves 99 percent of requests within 24 hours.
Allowing patients to access drugs after Phase I clinical trials means more patients will be treated.	Many physicians and patients do not want to use IMPs that have only passed Phase I clinical trials.
Pharmaceutical companies worry that SAE or AE data from expanded access will negatively impact submission.	Expanded access cohorts operate on a different protocol and are for patients previously excluded from a trial.
The only factor that deters companies from granting expanded access are legal concerns.	Expanded access is complex and companies have to take several considerations into account before approving requests.

Improving Expanded Access

Improving the expanded access process is a goal for many companies, patients and physicians. One way to improve the process is to have increased patient involvement in formalizing the process and approving expanded access requests. Patient involvement will also help educate more patients about the process, any special considerations as well as why companies deny patient requests. Educating patients can also help encourage participation in clinical trials, and help patients understand the importance of testing new IMPs.

Centralizing and sharing information also could help support expanded access efforts. For example, companies could benefit from a centralized database that lists the approvals and regulations required for expanded access in a specific country. Aligning and harmonizing terminology across countries would also help to avoid confusion.

Finally, companies should consider using data from expanded access recipients to improve future clinical study outcomes. All opportunities to work with patients and assess treatment outcomes can impact future IMP protocols, and help companies maximize the benefits for their clinical trial.

With regulatory concerns, economic considerations, implications and resource constraints related to developing a formalized process, creating and maintaining an expanded access program is not simple. However, companies can learn from each other's mistakes and successes to help design a program that benefits both patients and companies.

For additional information on expanded access and guidance on designing a program, visit the FDA website: https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm

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