



Expanded Access Programs: Making Compassion Work

By Randolph Fillmore

This article discusses issues and efforts related to expanded access programs aimed at providing patients with quicker access to new and experimental drugs, many of which are potentially lifesaving. The perspectives of health authorities, industry and patients are explored as well as the historical legal and ethical issues involved in ensuring expanded access drugs are safe and efficacious.

Introduction

In the late 1980s and early 1990s, the HIV/AIDS emergency prompted the creation of a process by which those affected with HIV could receive drugs not yet approved by the US Food and Drug Administration (FDA) through an “expedited drug development” process and shortened clinical trials. In an early step, FDA established the AIDS Coordination Staff in 1988 to integrate the agency’s various AIDS-related activities and to interact with other agencies as well as outside groups interested in AIDS drug development. In the same year, FDA announced immediate implementation of a formal plan to reduce the time required for human testing of drugs for serious diseases, such as AIDS, Parkinson’s disease and certain aggressive cancers. The new “expedited development” process sought to eliminate Phase 3 clinical trials for drugs already shown to improve survival.^{1}

Expanded Access Today: FDA’s Perspective

According to Kevin Bugin of FDA’s Center for Drug Evaluation and Research (CDER), Office of New Drugs, converging forces created the impetus—as well as the evolution—of FDA thinking on Expanded Access (EA). Those converging forces included patients demanding greater access to options; legislative support for patient concerns; regulators seeking to meet patient demands but without undermining drug development activities;

manufacturers balancing their desire to help patients with the risks of drug development and physicians wanting to help their patients find options.

“Depending on the situation and the phase of development, different challenges exist related to the implementation of expanded access,” says Bugin. “But, experience also shows us that sometime opportunities exist to collect clinical data. To take advantage of the potential opportunities, one must consider them proactively. Expanded access truly integrated into drug development is too complex to implement ad hoc.”

The complexity of issues ranges from legal and regulatory, through drug development and business, to science and ethics.

Adverse Events Under EA

Bugin focuses on two important questions related to serious adverse events: “Do Serious Adverse Events (SAEs) under EA adversely affect drug development?” and “Do SAEs under EA affect regulatory review and action?”

His analysis of the first question looks at “clinical holds” on commercial Investigational New Drugs (INDs) and shows that during a 10-year period between 2005 and 2015, of 10,482 commercial INDs received, 831 (7.9%) were put on hold after the initial 30-day review and 1,033 of the 10,000+ commercial INDs were referenced by an EA program. Of the 1,033 referenced INDs during the same 10-year period, two (0.2%) were placed on hold, both based on deaths shortly after the drug was administered. In both cases, the holds were lifted after a short period of time after the cases were reviewed.^{2}

“FDA interprets safety events in the context in which they occur,” Bugin points out.

Looking at whether SAEs under EA adversely affect regulatory review, (regulatory action) data (collected January 2010 to December 2016) indicates there were 322 regulatory actions (positive-approval; negative-refuse to file or complete response) by FDA’s Office of New Drugs on 261 unique molecular entities and that 91 of those entities had been used in EA programs during drug development. Of those 91 actions, 15 were negative (EA was revealed as not responsible for the negative actions) and 76 were positive actions (approvals). In two positive action cases, safety data from EA was used to inform product labeling independent from the clinical trial experience. In one of those two cases, the approval was based solely on experience with EA.^{3}

“FDA recognizes that EA to investigational drugs is an important option for patients, so long as it does not interfere with clinical development,” concludes Bugin. “EA early in development could inform future trials and increase patient awareness and patient recruitment. Late in development EA could support the evidence of safety and efficacy. For rare diseases, EA may represent a unique opportunity for gathering evidence where prevalence is low-every patient counts.”

Industry Perspectives and Academic Collaboration

Agreeing with Bugin that EA, also known as compassionate use, are important ethical and public health issues, Raman Sonty, PhD, director, Global Medical Organization, Johnson & Johnson (J&J), explains that adjudicating such requests is a growing issue for companies developing medical products, particularly given both the increase in preapproval requests and the growing use of social media to leverage public opinion in support of such requests.^{4,5}

Individual patient appeals for compassionate use are usually very powerful, notes Sonty, given the personal stories and the urgency of the request. He adds that Janssen recognized the critical need for solutions and the J&J office of the Chief Medical Officer (CMO) decided to ‘stand up and stand out’ for patients and seek innovative solutions. This included partnering with New York University in implementing a pilot program to evaluate the value of an external, independent expert body in providing recommendations on compassionate use requests for the oncology drug, daratumumab.

Compassionate Use Advisory Committee (CompAC) Pilot

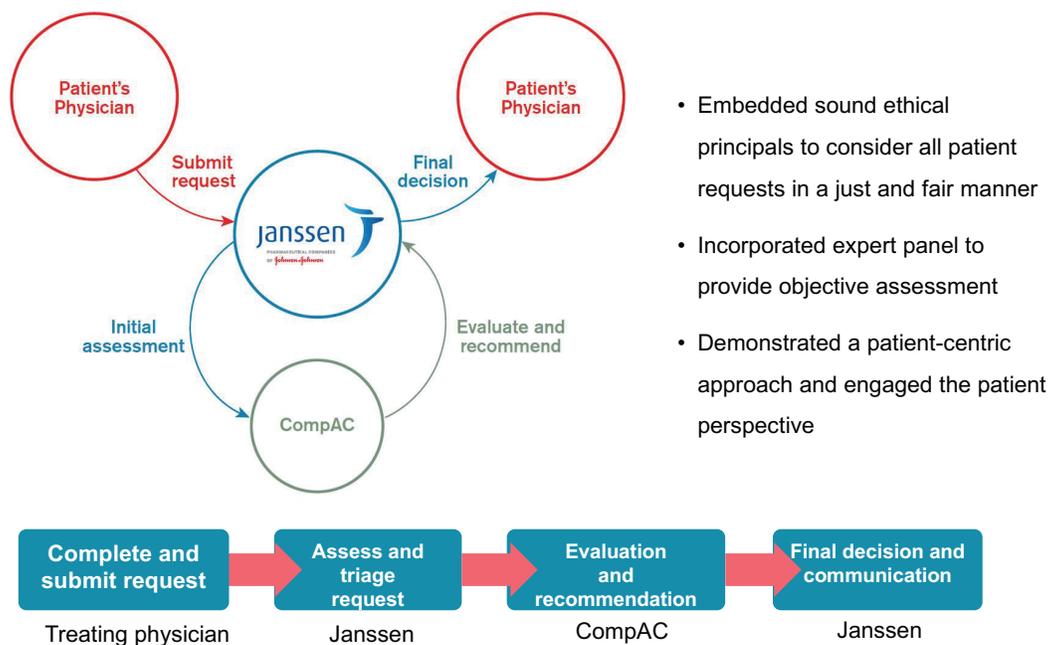
The CompAC was launched in May 2015 as a groundbreaking collaboration between industry (J&J) and academia (NYU’s School of Medicine) that sought to proactively embed

sound ethical principles into the consideration of compassionate use requests for investigational medicines.^{6}

“It ensures an evidence-based, transparent, patient-centric, fair and timely framework for independent evaluation of compassionate use requests by an international group of renowned medical experts, bioethicists and patient representatives,” says Sonty.

CompAC was initiated as a pilot program to assess the ability of an external, expert advisory committee to enrich decision-making for compassionate use requests for one investigational medicine, daratumumab. According to Sonty, the pilot achieved the objectives as defined within CompAC’s vision, mission, charter and bylaws that decision-making can be evidence-driven and patient-focused and guided by the ethical principles of beneficence, equality and transparency. The patient perspective was considered through patient advocates who participated in the CompAC pilot.

Figure 1. Compassionate use Pilot Between Academia and Industry



Based on an assessment of the results and overall positive experience of the pilot, J&J is expanding the pilot program to additional investigational medicines in its portfolio. According to Sonty, the innovative J&J/NYU CompAC model may serve others in the industry who want to bring its many benefits to patients.

“We were gratified that the pilot was greeted so positively by patients, caregivers and physicians,” says Sonty. “We set out to make a difference for patients and were happy to see that patients found our efforts valuable. At this time, we are further evolving the model to ensure its applicability across multiple therapeutic areas and diverse clinical settings.”

Making Compassion Work

Recognizing informational barriers to EA, Elena Gerasimov, director of programs for Kids V Cancer,^{7} explains how and why her organization developed their Compassionate Use Navigator program in 2016. According to Gerasimov, the navigator aims at assisting families and physicians by addressing informational barriers to expanded access, measuring unmet needs and determining outcomes of EA.

“Our Compassionate Use Navigator is designed to be a one-stop resource for navigating the process of applying for investigational drugs,” explains Gerasimov, adding that patients are often unaware of EA process. “The biggest hurdle for patients in getting access to investigational drugs is getting companies to agree to provide expanded access to their drugs.”

As her organization measures the need for investigational drugs, they find that compassionate use applications to FDA increased substantially from 2012 to 2016. She notes that in 2012, FDA received 870 applications and approved 857. By 2016, the number of applications received had climbed to 1,589 and 1,583 of those were allowed to proceed. However, these numbers include only those requests that have been granted by drug companies. The number of denied patient requests is unknown.

The Compassionate Use Navigator provides step-by-step guidance for physicians and patients who want to apply to a drug manufacturer, FDA or an Institutional Review Board (IRB) for compassionate use. The website provides information on the process, FDA contact information and links to necessary forms, such as FDA Form 3926 for reporting the patient's clinical history. The site also provides links to Kids V Cancer staff who can provide personal assistance with the process. Other information on the navigator site include lists of precision medicine clinical trials and recent news about EA developments.

"If you work at a drug company, you know that only a small percentage of drugs completing Phase 1 trials will eventually be approved," explains Gerasimov. "But, if you are a patient, you know that there are drugs approved every year that really help people. And, you know that those drugs once were unavailable because they have not yet been approved. Compassionate use is an attempt to fix a real problem, we just do not know how big it is. I believe that there is a strong need for data about the scale of demand."

Gerasimov, who notes that FDA authorizes compassionate use in more than 99% of cases, sees a number of challenges remaining and necessary next steps in increasing not only knowledge about expanded access, but also in identifying investigational drugs and providing incentives for manufacturers to provide compassionate use.

"We need to create incentives for drug companies to make more progress on pre-approval access," she adds. "One idea is for FDA to make it easier to use evidence from EA to supplement more traditional evidence that is used to gain approvals. "We need to educate sponsors about how EA can generate valuable data and how FDA views the adverse events; and to inform patients and physicians about their options. "

Currently, there is no easy way for physicians and patients to find out what drugs are in development. While this information is available on manufacturers' websites, there is no easily accessible, searchable public database, she says.

According to Gerasimov, it isn't possible to create appropriate solutions if we do not know the need for compassionate use drugs and what risks patients are willing to take to receive access.

"The first challenge is in informing physicians and patients about the compassionate use option," concludes Gerasimov. "The second challenge is in helping people negotiate the process—that's why we developed our Compassionate Use Navigator."

Conclusion and Policy Recommendations

Information is important. To help provide up-to-date information, the Regan Udall Foundation for the FDA launched its own Expanded Access Navigator in July 2017.^{8}

For some, EA is still a "work in progress" and issues remain with physicians, patients' groups and others lining up on either side of the issue. For some, EA is in need of further expansion. Opinions are divided. Agendas often conflict. It can become emotional.

For example, in July 2017 the Government Accountability Office (GAO) released a report on EA-related efforts by FDA on this issue.^{9} The GOA said:

"FDA's expanded access program allows patients with serious or life-threatening illnesses access to certain drugs before it has approved them. FDA also requires that manufacturers submit data about adverse reactions to these drugs. While FDA has provided some guidance to manufacturers, FDA does not fully explain the few instances when it would use these data on adverse reactions. This may influence manufacturers' decisions to give these drugs to patients due to concerns that adverse reactions will result in FDA placing a hold on their drug. To help FDA meet its goal of facilitating expanded access to investigational drugs by patients with serious or life-threatening diseases or conditions, when appropriate, the Commissioner of FDA should clearly communicate how the agency will use adverse event data from expanded access use when reviewing drugs and biologics for approval for marketing and sale in the United States."^{10}

FDA implemented the above recommendation from the GAO{11} and in complying with this request, issued clarification on how AE data will be used in its guidance updated in October 2017.{12}

Legislative Efforts Ramp up

In late March, the US House of Representatives passed (after having voted it down a week before) “right-to-try” legislation allowing seriously ill patients to bypass FDA to get access to experimental treatments.{13} The bill was passed 267-149 after having been defeated earlier. In a letter to House leaders, more than 75 patient advocacy groups, including the lobbying arm of the American Cancer Society, opposed the bill.

In a *New York Times* Op-Ed published just after the “Right to Try” legislation was passed, Katie Thomas sorted out some of the issues associated with expanding EA.{14} According to Thomas, “at first glance” a bill that would allow terminally ill patients access to experimental drugs “seems like the kind of thing anyone could get behind.” However, Thomas notes that the legislation is an effort to by-pass the approval of the US Food and Drug Administration, a regulatory body that approves 99% of the EA applications it receives.

“The right-to-try measures are opposed by a broad coalition of groups, which contend the bill will not help patients and will undermine the authority of the primary regulatory agency, the FDA,” writes Thomas. “Four former FDA commissioners, including two each from the democratic and republican administrations, oppose the bill, as do dozens of patient groups, including the American Cancer Society Cancer Action Network and the American Lung Association.”

Thomas concludes by saying that drug companies with experimental drugs “worry that the logistical work of granting access could slow efforts to get the drug approved,” and when it would become available to any patient who needed it.

Over the past few years, practical, legal and ethical issues also have been considered by clinicians and academics.

For example, a 2015 article published in the *New England Journal of Medicine*, “Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs,” (Jonathan J. Darrow, et al) makes policy recommendations and raises some cautionary issues regarding EA. “The ethical and policy debate on the appropriate balance between access to and protection from potentially useful but also possibly harmful or ineffective medicines began with the passage of the Pure Food and Drug Act in 1906. The escalation of the battle over EA has rekindled this debate a century later. In the ensuing years, Congress has unambiguously delegated authority over striking this balance to FDA, but growing antiregulatory sentiment has begun to threaten this assumption, with the most persuasive arguments being made concerning patients with terminal illnesses who appear to have much to gain and little to lose by accessing unapproved drugs. However, this debate will need to take into account the simple concept that led to the regulatory authority of FDA in the first place: that it may well not be in the interest of patients, however sick they may be, to have easier access to products that are ineffective and may actually worsen their clinical status.”{15}

Note: this article was based in part on presentations given at the 2017 Drug Information Association’s Global Annual meeting held 17-21 June in Chicago, IL. As the topic evolves, follow up articles will be published.

References

1. Institute of Medicine. 1991. *Expanding Access to Investigational Therapies for HIV Infection and AIDS*. Washington, DC: National Academies Press. <https://doi.org/10.17226/1778>. Accessed 17 April 2018.
2. Rosenblatt M and Kuhlik B. “Principles and Challenges in Access to Experimental Medicines.” *JAMA*. 2015; 313:2023-2024.
3. Jarow J P, Moscicki R. Impact of Expanded Access on FDA Regulatory Action and Product Labeling. *Therapeutic Innovation & Regulatory Science*. 2017.
4. Caplan, A L and Ray A. “The Ethical Challenges of Compassionate use.” *JAMA*. 2016; 315:979-980.
5. Caplan, A L, Bateman-House A, et al. “A Pilot Experiment in Responding to Individual Patient Requests for Compassionate Use of an Unapproved Drug: The Compassionate Use Advisory Committee (CompAC).” *Therapeutic Innovation and Regulatory Science*. 1-6 2018
6. A Pioneering Partnership to Bring Fairness to “Compassionate Use” Requests. NYU website. <https://med.nyu.edu/pophealth/newsevents/awards-recognition/pioneering-partnership-bring-fairness-compassionate-use-requests>. Accessed 17 April 2018.
7. Compassionate Use Navigator. Kids V Cancer website. <https://www.kidsvcancer.org/compassionate-use/>. Accessed 17 April 2018.

8. Regan Udall Foundation for the FDA. <http://navigator.reaganudall.org/expanded-access-navigator>. Accessed 17 April 2018.
9. Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used. GAO website. <https://www.gao.gov/products/GAO-17-564>. GAO website. Accessed 17 April 2018.
10. Ibid.
11. Op cit 9.
12. Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers. Guidance for Industry. FDA website. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf>. Accessed 17 April 2018.
13. House Passes 'Right to try' Drug Bill. The Hill website. <http://thehill.com/policy/healthcare/379580-house-passes-right-to-try-drug-bill>. Accessed 17 April 2018.
14. Thomas, K. "Why Can't Dying Patients Get the Drugs They Want?" March 2018. <https://www.nytimes.com/2018/03/23/health/right-to-try-drugs-fda.html>. Accessed 17 April 2018.
15. Darrow JJ, Sarpatwari A, Avorn J and Kesselheim AS. *New England Journal of Medicine*, 2015; 372:279-286.

About the Author

Randolph Fillmore is a technical writer for Florida Science Communications, Inc.

Cite as: Fillmore R. "Expanded Access Programs: Making Compassion Work." *Regulatory Focus*. April 2018. Regulatory Affairs Professionals Society.

© 2018 by the Regulatory Affairs Professionals Society. All rights reserved.