

Individual Compassionate Use: Concerns for Drug Manufacturers Considering Participation

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The FDA's recent issuance of a draft guidance and streamlined form entitled "Individual Patient Expanded Access Applications: Form FDA 3926" provides an excellent opportunity to revisit the current statutory and regulatory requirements for expanded access (also called "compassionate use") requests, examine the FDA's rationale behind this new guidance and streamlined form, and ponder some cautionary points and ethical concerns that pharmaceutical manufacturers should weigh before deciding to honor these expanded access requests. This article will also analyze the new role of mainstream media reports and social media campaigns in influencing expanded access participation by manufacturers and consider Congress' bipartisan draft "21st Century Cures Act," which would establish new expanded access requirements for expedited FDA approval, create an expanded access task force, and require the FDA to finalize their May 2013 draft guidance on expanded access.

Current Statutory and Regulatory Requirements

By Harold M. Bishop, J.D.,
Health Law Senior Writer Analyst

Section 561(b) of the federal Food, Drug, & Cosmetic Act (FDC Act) ([21 U.S.C. §360bbb\(b\)](#)) provides that any patient, acting through a physician, may request from a drug manufacturer or distributor, an investigational new drug (IND) for the diagnosis, monitoring, or treatment of a serious disease or condition if:

- the treating physician determines that there is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the disease or condition involved, and the probable risk to the person from the IND is not greater than the probable risk from the disease or condition;
- the FDA determines that there is sufficient evidence of safety and effectiveness to support the use of the IND;
- the FDA determines that provision of the IND will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and
- the sponsor (generally the company developing the IND for commercial use) or clinical investigator submits a clinical protocol (a document that sets forth the treatment plan for the patient) to the FDA describing the use of the IND that is consistent with the FDC Act and applicable FDA regulations.

On August 13, 2009, the FDA published a Final rule ([74 FR 40900](#)) amending its IND regulations on expanded access by adding a new subpart I to 21 C.F.R. part 312, which describes expanded access for individual patients, including for emergency use. The FDA expressly intended the Final rule to: (1) increase awareness of expanded access programs and the procedures for obtaining INDs for treatment of patients; and (2) facilitate the availability of INDs for treatment use, while protecting patient safety and avoiding interfer-

ence with the development of INDs for marketing under approved applications.

The four expanded access criteria contained in section 561(b) of the FDC Act are specifically set forth in new subpart I at 21 C.F.R. [secs. 312.305\(a\)](#) and [312.310\(a\)](#). The regulations allow a physician to satisfy some of the FDA submission requirements for expanded access by referring to information contained in an existing IND held by the manufacturer, if the physician obtains permission from that IND holder. If permission is obtained, the physician then provides the FDA a letter of authorization (LOA) from the existing IND holder that permits the FDA to reference that IND.

Section 312.305(b) sets forth the submission requirements for all expanded access uses, including requests for an individual patient. One of the requirements is that a “cover sheet” be included. The cover sheet currently required is [Form FDA 1571](#), which was originally designed for manufacturers seeking FDA approval to begin human testing, not for physicians seeking use by individual patients. Form FDA 1571 calls for 26 separate types of information and seven attachments and, according to FDA estimates, takes eight hours to fill out for an individual patient expanded access request and 16 hours for an individual patient expanded access emergency use request.

In an interview with Wolters Kluwer Law & Business (WK), [Amy K. Dow](#), a member of [Epstein Becker & Green’s Health Care and Life Sciences Practice](#) in Chicago, indicated that “the current statutory and regulatory provisions provide an appropriate framework to allow individual patient access to investigational products.” Dow noted, however, “the process...is burdensome and requires a substantial commitment on the part of the treating physician.” Dow added “much of the information currently required to be submitted to FDA is of limited relevance in the context of compassionate use by an individual patient, but was intended for use in approving clinical trials sponsored by product manufacturers seeking approval of their products.” Dow also believes that this burden may deter some treating physicians from making an expanded access request for a patient.

[David Farber](#) and [Preeya Noronha Pinto](#), partners in the Washington, D.C. law firm [King & Spalding](#), took a slightly different view during an interview with WK. According to Farber and Pinto, “the existing statutory and regulatory regime is sufficient, as far as it goes. In other words, to the extent that the FDA continues to be the ultimate approval authority for an

individual expanded access request, which it should be, the existing statutory and regulatory requirements are sufficient.” Farber and Pinto, however, believe “neither federal statute nor regulation can address what [they] see as the real challenge to both patients and manufacturers, which is the central, yet undefined and unregulated, role that biopharma manufacturers play in the individual expanded access process, and the inability of even the most sophisticated companies to face international pressures from social media campaigns to provide access in even the most inappropriate of cases. Further, none of the existing statutory, regulatory or other regimes fully accounts for the role of trained ethicists to participate in decision-making.”

New Draft Guidance and Form FDA 3926

The FDA also has expressed concern that its goal of facilitating access to drugs for individual patient treatment use may have been complicated through difficulties experienced by physicians in submitting Form FDA 1571 and associated documents. [According to Peter Lurie](#) M.D., M.P.H., Associate FDA Commissioner for Public Health Strategy and Analysis, after hearing “concerns from patients and physicians that the process for gaining access to investigational drugs was too difficult,” the FDA “pulled together a team to find a way to make that process simpler” by assigning a special working group the task of “designing a form more suitable for use by a physician not necessarily familiar with the IND process. The agency therefore tasked a special working group with designing a form more suitable for use by a physician not necessarily familiar with the IND process.”

The result of the special working group’s efforts is the introduction of a [draft guidance](#) entitled “Individual Patient Expanded Access Applications: Form FDA 3926,” that, when finalized, should streamline and accelerate individual patient expanded access to INDs. Draft Form FDA 3926 is shorter than Form FDA 1571 and requests only the following information:

1. patient’s initials and date of submission;
2. clinical information;
3. treatment information;
4. an LOA from the IND manufacturer, if applicable;
5. the physician’s qualifications;
6. the physician’s contact information and IND number, which is not the same as the manufacturer’s IND number;

7. a request for authorization to use draft Form FDA 3926, when finalized, for individual patient expanded access applications instead of Form FDA 1571; and
8. a certification statement and physician's signature.

The FDA estimates that Form FDA 3926 will take only 45 minutes to fill out.

As discussed in the draft guidance, the FDA intends to accept submission of Form FDA 3926 as full compliance with the IND submission requirements under [21 C.F.R. part 312](#). To the extent that information required under part 312 is not contained in Form FDA 3926, however, the FDA intends to consider its submission, with item number 7 (described in the above paragraph) checked and the form signed by the physician, to constitute a request to waive any other applicable application requirements, including additional information included in Form FDA 1571 and [Form FDA 1572](#) (Statement of Investigator, providing the identity and qualifications of the investigator conducting the clinical investigation).

The draft guidance also provides, in an emergency situation, that the request to use the IND for individual patient expanded access may be made by telephone (or other rapid means of communication) to the appropriate FDA review division. In addition, under 21 C.F.R. sec. 312.310(d), authorization for emergency use may be given by the FDA official over the telephone, provided the physician explains how the expanded access use will meet the requirements of sections 312.305 and 312.310 and agrees to submit Form FDA 3926 within 15 working days of FDA's telephone authorization of the expanded access use.

Farber and Pinto consider the draft guidance and new Form FDA 3926 welcome developments because they simplify and streamline the application process; however, they believe that the "simplification of the application does not get to the heart of the problem facing all stakeholders in the individual expanded access arena—the clash between the individual's perceived need for access to experimental medications, and the manufacturer's challenges in providing access when it is medically appropriate."

Dow also agreed that the draft guidance and the new streamlined application represent a "logical, common sense approach" and "[are] likely to have a significant, positive impact on the burden associated with individual patient expanded access applications." Dow cautioned, however, "[a]n uptick in the number of requests for expanded access may...present challenges to drug makers who may not be in a position to provide access to their investigational products due to limitations on supplies of the product or for other reasons."

Cautionary Points for Drug Manufacturers

While the FDA usually works closely with drug manufacturers to facilitate wider access to a drug, it is ultimately the sole choice of a drug manufacturer or distributor whether to grant expanded access to an IND. In making

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– Amy K. Dow
Member, Epstein Becker & Green

a decision to grant expanded access, the manufacturer should consider a variety of factors, including:

1. possible accusations of off-label use;
2. the removal of incentives for patients to enroll in clinical trials;
3. the creation of new adverse events;
4. drug cost;
5. the strain on staff resources and the possible need for additional infrastructure;
6. charging patients for the drug; and
7. that little is usually learned about a drug from single patient use.

Off-label use. Although previous FDA guidance, entitled "[Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices](#)," addressed the need for drug manufacturers to only respond to physicians' unsolicited requests for more off-label information, it failed

to address the possible exposure that is created by a situation in which a manufacturer makes public the existence of expanded access programs for patients populations or advocacy groups.

As a result, [Leslie M. Tector](#), J.D., a member of the Health Law Practice Group at [Quarles & Brady](#), cautioned drug manufacturers that making public the existence of expanded access programs could be seen as solicitation of illegal off-label promotion of drugs that have not been approved by the FDA as safe and effective, resulting in fines and penalties. Tector [recommended](#) that drug manufacturers consider the following when creating internal processes to grant expanded access requests.

- Companies should not permit the sales organizations to promote expanded access programs.
- Medical Affairs should be the point for all requests and should consider eligibility for existing clinical trials when request are made.
- Companies should have a mechanism to allow Medical Affairs to coordinate with regulatory and legal departments to allow for rapid decision making and proper documentation of the basis for a decision to honor a request, and to ensure that all legal and regulatory requirements are satisfied.
- Companies should consider whether regulations permit the patients or their insurers to be charged for the cost of the investigational drug, as well as the administrative costs associated with assisting in drafting a treatment protocol, monitoring the investigational use, and shipping the investigational agent.

Removal of incentives for patients to enroll in clinical trials. According to [Alexander Gaffney](#), RAC, manager of the Regulatory Intelligence Group at the Regulatory Affairs Professional Society (RAPS), drug manufacturers are concerned that expanded access programs could remove the incentive for patients to enroll in clinical trials designed to accumulate the clinical evidence necessary for their drug's full FDA approval. Removal of this incentive could thereby delay its full FDA approval, which could ultimately harm other patients.

Creation of new adverse events. Gaffney also indicated that drug manufacturers are concerned that the removal of the IND from tightly controlled and heavily monitored environments could subject the drug to incorrect use and previously unknown adverse events, which would need to be reported to FDA. In addition, as far back as 2001, Robert J. Temple, M.D., former Associate Director for the FDA's Center for Drug Evaluation and Research (CDER), [testified](#) before the

House Committee on Government Reform that "the use of an investigational drug in a less controlled setting, in patients with very advanced disease could lead to adverse reactions that might raise difficult to resolve but spurious safety concerns about the drug." As a consequence, these new adverse events could raise questions for regulators, again delaying FDA approval and hurting the chance of an IND getting to market to help others.

Farber and Pinto also believe that data resulting from expanded access use could adversely impact the manufacturer's clinical trials and that it is an important issue for a manufacturer to consider before agreeing to expanded access to its investigational drug. According to Farber and Pinto, "notwithstanding FDA's claims to the contrary, there have been instances in which [adverse data] has been an impact [to clinical trials]."

Drug costs. In his House testimony, Dr. Temple also indicated that providing expanded access may be difficult for a drug manufacturer because "the batches prepared for early drug studies are usually small; making larger amounts available is expensive and not considered reasonable until there begins to be evidence that the drug is of value." Gaffney wrote that cost is "a problem most evident in small biotechnology startups which do not yet have any income." Farber and Pinto agreed that cost is an issue to be considered, "particularly in the case of a small company making limited doses of a complex biologic."

Staff resources. Internal drug manufacturer staff also can be stressed by expanded access requests. Dr. Temple testified, "the process of individualized packing and shipping of drugs for single patient use on an emergency basis can be very disruptive to departments that are organized to pack and ship drugs in a scheduled manner for clinical trials." In addition, as Tector stated with regards to off-label use, a company's Medical Affairs department should take on the duty of expanded access requests and should "coordinate with regulatory and legal departments to allow for rapid decision making, proper documentation of the basis for decision to honor a request, and ensure that legal and regulatory requirements are satisfied." These additional Medical Affairs duties will undoubtedly mean time away from their other internal staff duties.

Drug supply concerns. Gaffney noted that "there are also concerns that expanding access use will result in there not being enough drug product available to supply both existing trials and new clinical trials." According to a [statement](#) by the Biotechnology Industry Organization (BIO) on compassionate use, the concern over adequate drug supply exists because IND manufacturers are often put in the difficult situation of "trying to balance an

individual's early access to a drug still in clinical trials against the company's obligation to develop drugs for larger groups of patients and ensure that these products gain regulatory approval as quickly as possible." BIO further stated, "companies often have to address the challenge of equitable distribution of limited drug supply to a large number of patients in need. These decisions are particularly difficult and heart-wrenching when we know the personal stories of the individual patients."

Dow also expressed her concerns about drug supplies, stating that expanded access programs may "consume limited supplies of often costly investigational products without providing the level of meaningful data that accompanies use of an investigational product in the context of a clinical trial."

Charging compassionate use patients for INDs.

A [May 2013 FDA draft guidance](#), entitled "Charging for Investigational Drugs under an IND—Qs & As," confirmed that drug manufacturers may charge for individual expanded access INDs as long as they:

- provide the FDA reasonable assurance that charging will not interfere with drug development (21 CFR sec. 312.8(c)(1)); and
- in its charging request submission, provide documentation to show that its calculation of the amount to be charged is consistent with the requirements of 21 CFR sec. 312.8(d). The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculation (21 CFR sec. 312.8(d)(3)).

Therefore, for individual expanded access requests, the sponsor may charge the patient only for the direct costs of providing the drug. The direct costs are defined as those that are specifically and exclusively attributable to providing the drug to clinical trial subjects (21 CFR sec. 312.8(d)(1)). These include costs to manufacture the drug in the quantity needed to conduct the clinical trial for which charging has been authorized or costs to acquire the drug from another source, and costs to ship and handle (e.g., store) the drug.

Some companies, however, may be wary of charging patients for the IND. Gaffney quotes a former FDA official involved in overseeing the compassionate use program as saying that some companies believe that charging a "reasonable" amount for an IND may impact their ability to negotiate a higher sale price for the drug at a later date.

Ethical Concerns

BIO's Board Standing Committee on Bioethics issued a "[Points to Consider](#)" document in April 2010, to

help members analyze the many ethical challenges raised by early access programs. It must be pointed out that these Points to Consider do not represent BIO policy, but were intended for informational purposes and to further early access program debate. The points are: (1) a patient's right to treatment based on his or her autonomous decision-making ability does not supersede a company's ethical responsibility

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Partners, King & Spalding

to develop and market safe and effective products as fast as possible; (2) early access programs could hurt the integrity of the clinical trial process; (3) a patient suffering from a life-threatening illness may not be able to provide consent that is truly informed when receiving a product under an early access program; and (4) if a company makes unapproved products available outside of a clinical trial, it must ensure equity in distribution.

Patient autonomy v. responsibility to develop safe and effective products. Terminally ill patients have sometimes claimed that they have the privacy and liberty rights to access to an unapproved drug product outside of a clinical trial if they or their physician believe it will treat their condition and they understand the potential

risks of taking the product. Under federal law, they do not have such rights.

These rights were litigated in *Abigail Alliance v. von Eschenbach*, a case in which the Alliance sued to enjoin the FDA from barring the sale of post-Phase I Clinical Trial drugs to terminally ill patients not enrolled in clinical trials. In granting the FDA's motion to dismiss, the district court held that the Alliance failed to state a valid fundamental right to access and the FDA's policy bore a rational relationship to the legitimate state interest of public health. A three-judge panel of the D.C. Circuit reversed the district court, but restricted its holding to terminally ill mentally competent adult patients for whom existing government-approved treatments were ineffective. A full panel of the D.C. Circuit, however, reversed the three-judge panel, holding that there was no fundamental right for terminally ill patients to access post-Phase I investigational new drugs. The U.S. Supreme Court refused to hear the case.

With no individual right to expanded access under *Abigail Alliance*, the BIO Points to Consider defined the question as: "balanced against an individual's right to decisional autonomy is the company's ethical obligation to develop drugs for larger patient populations and to ensure these products meet regulatory approval as quickly as possible." For example, should an adverse event occur during individual expanded access use, the FDA might require the company to initiate new clinical trials, which could delay or prevent FDA approval of the IND. Therefore, according to BIO points, "the question often confronting companies is whether to put an entire project at risk—and therefore jeopardize availability of a drug for a larger patient population – in order to provide early access to a product for an individual or small group of patients."

Farber and Pinto defined the issue as one of population v. individual health. They asked "should a company draw a line in the sand and reject all requests given that the drug development and approval process is focused on impacting populations and not individuals (a harsh reality, but one that several sophisticated companies seriously evaluate)?"

Dow put it this way: "[while] the desire to provide access to an investigational drug to an individual for whom there appears to be little hope for treatment may be compelling, manufacturers must balance the interests of the individual with the greater good of making the approved drug available to any patient who needs it through the FDA approval process. Therefore, manufacturers must be mindful of the impact of providing expanded access on their ongoing clinical development activities."

Integrity of the clinical trial process. Clinical trials test potential treatments in human volunteers to see whether they should be approved for wider use in the general population. The FDA is committed to protecting the participants of clinical trials, as well as providing strict safety and effectiveness standards. The agency requires that reliable information is provided to those interested in participating in clinical trials so that they will understand the risk involved.

The fear, according to BIO, is that "if patients knew they could access products prior to approval outside the clinical trial process, it reduces their incentive to enroll in a trial especially since they may receive a placebo and therefore not be treated for their illness. Therefore, if early access programs become extremely common, the clinical trials system could break down, delaying or ending some product development programs."

Truly informed consent. Expanded access use requires that patients provide informed consent about the potential risks and benefits of an investigational product. The question is whether there is sufficient safety data available for an expanded access user to make an informed choice. BIO believes that "[c]ompanies developing an early access program for a product must be confident that such data exists. They must also be careful that patients not get false hope from early product data."

"Manufacturers are typically the most knowledgeable about their development-stage products, and should use that knowledge to assess the risks and benefits of the expanded access use by a specific patient," according to Dow. Therefore, "if the investigational product is unlikely to benefit a patient in light of the patient's prior therapies or disease progression, or if the risks associated with use of the product by the patient substantially outweigh potential benefits for that patient, a manufacturer may consider declining the request."

Ensuring equity in distribution. In considering whether to allow expanded access of an IND, a company should establish an equitable process and criteria for determining which patients should have access to it. According to BIO, "certain patients may have an advantage over others because they know about early access programs, have hired outside counsel, or are particularly knowledgeable about research activities for a particular disease. None of these establish that patient as more deserving of early access to a product than others." If an equitable process and criteria cannot be developed, BIO suggests that the company re-consider whether to establish the program.

Effects of Mainstream Media Reports and Social Media Campaigns

Farber and Pinto believe that a very important development in the expanded access process is the role of mainstream media reports and social media campaigns and how they are influencing behavior by all participants in the process.

As an example, Farber and Pinto pointed to the March 2014 story of seven-year-old cancer patient, Josh Hardy, whose parents' interview with CNN launched a nationwide social media campaign to pressure drug manufacturer Chimerix to provide Josh with brincidofovir, an investigational antiviral drug for the treatment of a cytomegalovirus, adenovirus, smallpox, and ebolavirus infections.

After CNN reported that Josh was suffering from adenovirus, "was in heart and kidney failure, and vomited blood several times an hour as his family held a vigil in the intensive care unit of a Memphis hospital," intense pressure from social media began.

According to a Washington Post article entitled "Crowdsourcing medical decisions: Ethicists worry Josh Hardy case may set bad precedent," "after several days of intense phone calls with officials at the FDA's Division of Anti-Viral Products—who heard about Josh's plight through the media—they worked out a solution. Instead of getting the drug through the compassionate-use program, Josh got it through the clinical trial process. Although he wasn't eligible for the trial in progress—it is for adults with a different condition—the FDA offered to immediately green-light a new clinical trial that would be designed for pediatric patients with Josh's condition." This solution allowed Chimerix to give the medication to Josh and several other children at no cost. After just three doses of brincidofovir, Josh was sitting up, doing homework and playing board games with his brothers, according to CNN.

The chief executive of Chimerix, Kenneth Moch, told the Washington Post "that until 2012 the company had a large compassionate use program but had to discontinue it to focus its limited resources—it has only 60 employees and is not profitable—on getting the drug approved."

In the last two years, Chimerix received 200 applications for compassionate use (80 were for adenovirus infections) and all of the requests were turned down, according to the Post. Moch explained that, "every one of those [refusals] is heart-wrenching. But making

it available for one child, whatever the reason, as an exception is not equitable distribution."

Farber and Pinto share Moch's concerns. They believe that "the Josh Hardy story will not be the last national social media campaign, and in such instances we have seen medical judgment, ethics, clinical trial considerations, and even cost considerations overtaken by social media and mainstream media attacks (and, in that case, actual death threats to executives). If there is one risk to

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– Robert J. Temple, M.D.,
Former Associate Director for the FDA's
Center for Drug Evaluation and Research

the entire process, it is the success of these campaigns and the threat they pose to manufacturer willingness to even engage in expanded access conversations."

Congress Explores 21st Century Cures

It has been reported that among the 10,000 known diseases, 7,000 of which are considered rare, there are treatments for only 500. As stated by Dr. Francis Collins, Director of the National Institutes of Health: "Developing a drug takes time and money: on the average, around 14 years and \$2 billion or more. More than 95 percent of the drugs fail during development."

In April 2014, the House Energy and Commerce Committee Chairman Fred Upton (R-Mich) partnered with Rep. Diana DeGette (D-Colo) to conduct a comprehensive bipartisan look at this problem. Over the course of the last year, the committee had wide-ranging conversations with patients, providers, innovators, regulators, and researchers from around the

Expanded Access IND Submissions to FDA (2010 to 2014)					
	2014	2013	2012	2011	2010
Emergency:					
Individual (Single) Patient INDs received	1096	315	289	443	516
Individual (Single) Patient INDs allowed to proceed	1096	313	287	442	500
Non-Emergency:					
Individual (Single) Patient INDs received	696	550	498	652	484
Individual (Single) Patient INDs allowed to proceed	692	550	496	652	484
Intermediate Size Patient Population:					
Intermediate INDs received	52	28	14	0	2
Intermediate INDs allowed to proceed	50	27	14	0	2
Treatment:					
Treatment INDs received	0	0	0	1	0
Treatment INDs allowed to proceed	0	0	0	1	0
Totals:					
Total Expanded Access INDs received by FDA	1844	893	801	1096	1002
Total Expanded Access INDs allowed to proceed by FDA	1836	890	797	1095	986
Total Expanded Access INDs denied by FDA	8	3	4	1	16

The FDA's data indicate that between 2010 and 2014, it rejected just 32 of 5,636 expanded access INDs. To put it simply, from 2010 to 2014, the FDA only denied 0.5 percent of all the expanded access IND applications it received. The majority of rejections (21) were related single-patient emergency INDs. In addition, the number of requests in 2014 (1844) were more than double the number in 2013 (893).

country. After a year of listening, on January 26, 2015, the Committee issued a 393 page draft [21st Century Cures Act](#) (Cures Act) with the intent of continuing this national dialogue.

Public availability of expanded access policies. The Cures Act would amend section 561 of the FDC Act (21 U.S.C. §360bbb) to require that not later than 30 days after the date on which the drug meets the definition of a covered investigational drug (defined as a designated breakthrough therapy, qualified infectious disease product, or an orphan drug), the sponsor of the covered investigational drug must submit to the FDA and make publicly available the policy of the sponsor with respect

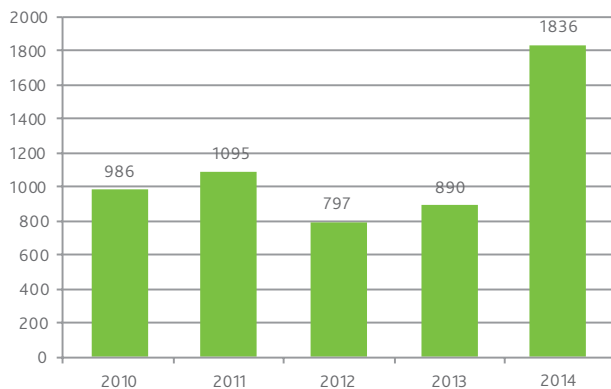
to expanded access requests. If the sponsor's policy indicates it intends to accept expanded access requests, the policy would have to include: (1) a single point of contact who receives and processes such requests; (2) procedures for making such requests; (3) the general criteria for the sponsor's consideration or approval of such requests; and (4) the amount of time the sponsor anticipates will be necessary to respond to such requests.

Prompt notice of denial. In the case of a manufacturer or distributor's denial of an expanded access request, the Cures Act would require the manufacturer or distributor to submit to the person (or physician) who made the request written notice of the denial, including an explanation for the denial, within five days of the denial.

Qualitative analysis. Not later than 180 days after enactment of the Cures Act, and every two years thereafter through 2023, the Comptroller General of the United States would be required to submit to the House and Senate a report containing a qualitative analysis of the extent to which individual patients have expanded access to investigational drugs and recommendations for improving such access. The report would be required to analyze the following:

- Whether there are any identifiable patterns in expanded access requests, such as the types of indications for which requests for individual patient access are sought or the reasons for the denial of such requests.

Expanded Access INDs Approved by FDA



- What the primary barriers are to drug sponsors granting requests for individual patient access.
- How the FDA evaluates safety and efficacy data submitted in connection with such requests.
- The amount of time that: (1) a physician typically takes to complete the paperwork necessary to make such a request; (2) a drug sponsor takes to process such a request and to issue a decision with respect to the request; and (3) the FDA takes to process such a request and to issue a decision.
- How regulations, guidance, policies, or practices may be modified, streamlined, expanded, or discontinued to reduce or prevent delays in approving expanded access requests.
- The number of expanded access requests that, for the period covered by the report: (1) were approved by drug sponsors and the FDA; (2) were approved by drug sponsors but denied by the FDA; and (3) were denied by drug sponsors.
- How to encourage drug sponsors to grant requests for expanded access, including requests for emergency use, intermediate-size patient populations, and large patient populations under a specified indication.
- Whether and to what extent adverse events reported to the FDA as a result of individual use of an investigational drug affected the development or approval of any drug.

Expanded Access Task Force. The Cures Act would also require that the FDA create an “Expanded Access Task Force” to explore mechanisms for improving the access individual patients have to investigational drugs. The Task Force would be convened within 90 days the Comptroller General’s first biennial report.

The Task Force would be required to comprehensively evaluate the access individual patients have to investigational drugs, taking into account: (1) the unique challenges faced by children with likely fatal diseases for which there is not a comparable or satisfactory alternative therapy available; (2) possible incentives for biopharmaceutical companies and providers to approve requests submitted under such subsection; (3) ways to improve follow-up reporting of adverse event data and compliance with such reporting requirements; (4) how the FDA interprets and takes into consideration adverse event data from expanded use; (5) ways to streamline and standardize the process for submitting expanded access requests; and (6) the costs incurred by biopharmaceutical companies for the time, effort, and delivery of investigational drugs to expanded access patients for the diagnosis, monitoring, or treatment of a serious disease or condition.

Within 180 days of being convened, the Task Force would be required submit a report to the House and

Senate in an electronic format describing the specific recommendations of the Task Force for improving the access individual patients have to investigational drugs.

Finalizing drug guidance on expanded access. Not later than 180 days after the Task Force submits the report to the House and Senate, the FDA would be required to finalize its May 2013 draft guidance entitled “Expanded Access to Investigational Drugs for Treatment Use—Qs & As.”

The final version of the guidance would be required to: (1) clearly define how the FDA interprets and uses adverse drug event data from expanded use; and (2) take into account the report of the Expanded Access Task Force and the first report of the Comptroller General.

Farber and Pinto believe that a very important development in the expanded access process is the role of mainstream media reports and social media campaigns and how they are influencing behavior by all participants in the process.

According to the [House Energy and Commerce Committee](#), the Century Cures Act is just the beginning of the legislative process. The committee looks forward to continuing the important conversation about how the legislation can make a meaningful difference in the lives of patients and help maintain our nation’s standing as the world leader in biomedical innovation. The committee has invited shareholders to submit their specific suggestions to cures@mail.house.gov or contact committee staff with any questions.

Conclusion

While the current statutory and regulatory requirements for expanded access have served their purpose, the consensus seems to be that Form FDA 1571 takes too long to fill out and, according to Dow, much of the required information is geared to “clinical trials sponsored by product manufacturers seeking approval of their products.” As a result, Dow and others believe this

burden may deter some treating physicians from making an expanded access request for a patient.

Dow, Farber and Pinto all consider the new draft guidance and attached Appendix 1: Form FDA 3926 to be welcome developments that should simplify and streamline the expanded access application process. Dow cautioned, however, “[a]n uptick in the number of requests for expanded access may...present challenges to drug makers who may not be in a position to provide access to their investigational products due to limitations on supplies of the product or for other reasons.”

Before honoring an expanded access request, the drug manufacturers should weigh a variety of factors, including possible accusations of off-label use, the removal of incentives for patients to enroll in clinical trials, the creation of new adverse events, the cost of providing the drug, the strain on staff resources and the possible need for additional infrastructure, the question of whether to charge for the drug, and that little is usually learned about a drug from single patient use.

In considering these factors, Dow emphasized that “compassionate use programs are of limited benefit to manufacturers. They consume limited supplies of often costly investigational products without providing the level of meaningful data that accompanies use of an investigational product in the context of a clinical trial. Nonetheless, these programs allow manufacturers to give back to the patient communities that are dependent upon the manufacturers’ products.”

A variety of ethical questions also should be considered before expanded access requests are honored, such as balancing individual patient access with the responsibility to develop safe and effective products for the larger population, the integrity of the clinical trial process, whether a seriously ill or dying patient can actually give truly informed consent, and insuring equitable distribution of the drug to expanded access patients.

As pointed out by Farber and Pinto, the new role of mainstream media reports and social media campaigns in influencing expanded access participation by manufacturers has arrived and will likely have a profound effect on not only drug manufacturers and patients, but also the FDA, prescription drug plans, and our elected officials with oversight over the FDA. As described in the case of Josh Hardy, pressure was brought to bear not only on the drug manufacturer, but on the FDA, which

moved quickly to green-light a new clinical trial for pediatric patients with Josh’s condition.

Finally, these mainstream media reports and social media campaigns from the March 2014 Hardy case, and others, were undoubtedly heard by elected officials and may have been the final impetus behind the work that resulted in the bipartisan draft Cures Act, which began in April 2014. The Act goes quite far with its requirement that drug manufacturers publicly disclose their expanded access policy and set forth their procedures, general criteria for consideration or approval, and the amount of time they will need to respond. The Act’s qualitative analysis, the creation of the Expanded Access Task Force, and the requirement that the FDA finalize its May 2013 draft guidance, make it clear that Congress is serious about expediting access to investigation drugs for its seriously ill and dying constituents.

Nevertheless, before getting too excited about the new streamlined FDA form and guidance, and the potential legislative action, consider some very important cautionary words from Farber and Pinto. Remember that “every [expanded access] request is unique, and each needs to be evaluated on its own merits. Ultimately, manufacturers are in the business of providing care, and ethicists, executives, and medical professionals need to evaluate each case to determine whether the benefits outweigh the risks. On a macro level, there are dozens of manufacturers who are silent heroes – providing experimental drugs and providing real hope, and sometimes real cure (although the dearth of statistics as to how often and when remains a frustrating limitation). Similarly, there are some very difficult situations with no easy answers that provide heartbreaking anecdotes, but do not really contribute to solutions. Ultimately, this is a medical/ethical decision, which should be (and most often has been) private.”

The views expressed by David Farber and Preeya Noronha Pinto are theirs personally, and do not represent the views of King & Spalding or any of its clients.

The views expressed by Amy K. Dow are hers personally, and do not represent the views of Epstein Becker & Green or any of its clients.

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