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Implementation of 21st Century Cures Act Expanded Access Policies Requirements

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ABSTRACT

The US Food and Drug Administration (FDA) expanded access pathway allows patients with life-threatening or serious conditions to access investigational drugs outside of trials, under certain conditions. The 21st Century Cures Act ("Cures Act") requires certain drug companies to publicly disclose their expanded access policies. We characterized the proportion of applicable US bio-pharmaceutical companies, with an oncology related drug, implementing Cures Act requirements for expanded access policies and whether available policies contain the information described in the Act. We found about one-third of applicable biopharmaceutical companies (32%, 140/423) implemented the Cures Act requirement to have a public expanded access policy. Less than 1/3 of public policies contained all described information (31%, 44 /140). Larger companies and those with at least one drug receiving an FDA expedited designation (59% vs. 21%; $p < 0.001$), or at least one FDA-approved drug (57% vs. 28%; $p < 0.001$) were more likely to have a public policy. Our results suggest the Cures Act may be having a limited impact on its goals of supporting timely medical decisions and closing informational gaps for patients and doctors around expanded access to investigational oncology therapies, especially for products sponsored by smaller and newer companies.

INTRODUCTION

The United States (US) Food and Drug Administration (FDA) expanded access (EA) pathway, sometimes also called compassionate use, is a route for patients with immediately life-threatening or serious diseases or conditions to potentially access experimental medicines outside of clinical trials. To qualify, patients must be unable to enroll in a relevant clinical trial, have no comparable satisfactory alternative FDA approved therapy options, and be deemed more likely to experience benefit than risk from the unapproved intervention. Additionally, expanded access provisions should not threaten a product's development program (e.g., trial enrollment). Formalized in 1987, in the context of the AIDS epidemic, the expanded access pathway has been amended multiple times, most recently in 2016 through section 561 of the Food, Drug, and Cosmetics Act (FDCA), as a part of the 21st Century Cures Act ("Cures Act").

The Cures Act aimed to help increase awareness among patients and clinicians about the processes and procedures for accessing investigational medical products outside of clinical trials, by requiring certain drug companies to develop and publicly disclose their EA policies, for example, by posting them on their websites. The Act also describes five informational elements for the contents of the policies, related to who and how to contact the company with a request as well as the criteria and timeline used by the company for evaluating and responding to such requests. While having a publicly available policy does not guarantee a patient will ultimately receive a requested investigational oncology therapy, the Act aimed to increase the transparency and accessibility of company policies to better support physicians and patients in making timely medical decisions.[1]

While EA pathways can involve the participation of and approval from a physician, the FDA, and an institutional review board (IRB), the sponsor developing each product ultimately has a final gatekeeping power to grant or deny an access request. These sponsors are typically, though not always, biopharmaceutical companies, which vary substantially in size, revenue, and age. To date, only two studies have assessed implementation of the Cures Act requirements to have a publicly available EA policy. Reviewing small samples of 45 and 100 pharmaceutical companies, respectively, they found 76% and 47%, respectively, had publicly available expanded access policies. [2,3]

Our paper aims to extend these studies to newly include all drug companies headquartered in the US, with an oncology focus, that are highly likely subject to the Cures Act. This sample is defined

as US based companies with at least one oncology drug in or beyond Phase 2 in clinical trial development, or with at least one oncology drug that received a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy under subsection by the FDA. This scope expansion involves uniquely including all sized companies, private companies, companies without approved drugs but conducting or sponsoring an applicable phase 2 or later stage oncology clinical trial, and companies with at least one drug having received an FDA expedited program designation. We also review each publicly available expanded access policies for inclusion of the five categories of information described inclusion by the Cures Act and evaluate company characteristics, such as private versus public, size, and revenue, associated with having a publicly available EA policy.

We focus on companies with an oncology product for several reasons. First, oncology is the most common represented disease target for expanded access programs registered on clinicaltrials.gov through July 1, 2016.[4] Second, two new projects intended to improve the information available about EA were recently launched in oncology. The first is "Project Facilitate," a program run out of US FDA's Oncology Center of Excellence, which assists clinicians in navigating expanded access pathways for patients with cancer.[5] The second one, run by the Reagan-Udall Foundation for the FDA, is an expanded access navigator, providing a step-by-step guide for accessing investigational therapeutics geared toward patients and caregivers as well as clinicians.[1] While the navigator ultimately intends to cover multiple therapeutic areas, its initial phase was focused on oncology. We expect our findings will inform policymakers on oncology companies' transparency in terms of their expanded access policies and on information gaps in supporting doctors and patients in making informed and timely medical decisions.

METHODS

Data sources

Data were abstracted from Pharmaproject[6], a large commercial database of global pharmaceutical research and development, Medtrack, a commercial database of global pharmaceutical companies, and Crunchbase, an online database for companies.

Study Sample

We included all bio-pharmaceutical companies with a US headquarter and an oncology focus ("US based oncology companies"), that are highly likely subject to the Cures Act, which are generally companies with at least one oncology drug in or beyond Phase 2 in clinical trial development, or with at least one oncology drug that received a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy under subsection by the FDA. Companies without a US headquarter and subsidiaries of companies with US headquarters were excluded. See Table 1 for more company inclusion criteria and policy requirements under the Cures Act.

Data collection

We identified all applicable US-based oncology companies by searching Pharmaproject for US-based oncology drug companies with at least one oncology drug beyond Phase 2 in clinical trials, as well as those with at least one drug which received FDA expedited program designation. We then characterized drug companies by type (publicly traded or private), age, number of employees, annual revenue, and development status from Medtrack and Crunchbase. Unless otherwise noted, missing values were excluded from the analysis.

We manually searched every applicable company's website to identify and collect publicly available expanded access policies. If we could not find an expanded access policy on a company's website, we also conducted an internet search (using Google) and searched the FDA's Expanded Access Navigator for a public policy.[1] For the internet search, we used a company name followed by the following keywords: "expanded access," "compassionate use," "early access," and "pre-approval access" to find policies.

For available expanded access policies, we manually extracted policy characteristics, including the five pieces of information described for inclusion in policies by the Cures Act (see outcome measures). To ensure the robustness of our data, two research assistants conducted two independent data collections. We also extracted company characteristics, including company age, company type (publicly traded or private), number of employees, and annual revenue from Pharmaproject, Medtrack, and CrunchBase. All data were collected in June 2020.

Outcome measures

Our primary outcome measure was whether a drug company had a publicly available expanded access policy on its website. Secondarily, for available expanded access policies, we

assessed the proportion of policies containing five pieces of information described by the Cures Act related to: (1) whom to contact and (2) the process for requesting expanded access to a product at the company; (3) the anticipated time the company will take to acknowledge receipt of a request and (4) the criteria it will use to evaluate such requests; and, finally (5) whether the policy links to or references the clinical trial record on ClinicalTrials.gov (See Table 1 for more details).

In addition, we also examined 1) whether each company had a separate webpage for their expanded access policy, 2) how easily accessible the information was (i.e., number of clicks from the main webpage), 3) whether the policy followed the structure of one of the sample policy structures posted by the FDA on Expanded Access Navigator[7], and 4) terminology used for expanded access.

Finally, to assess whether company characteristics are associated with Cures Act implementation, we divided companies into groups: publicly listed vs. private companies; top 50% vs. bottom 50% in median annual revenue; top 50% vs. bottom 50% in median number of employees (large vs. small), top 50% vs. bottom 50% in median company age (older vs. newer). A detailed description of how we coded each variable is available in Appendix A.

Statistical Analysis

Frequencies and proportions are reported for our outcome measures. We used the Wilcoxon test to examine differences in the average value of compliance rate and counts of contents posted across two groups based on company characteristics. We reported the differences in mean alongside the 95% confidence interval and the two-sided P-value, which indicates statistical significance ($P < 0.10$ were considered as statistically significant). All statistical analyses were performed using Stata statistical software version 15.0 (StataCorp LLC).

RESULTS

Study Sample Characteristics

We identified 423 US-based drug companies with at least one oncology drug beyond Phase 2 in clinical development or which received FDA expedited program designation such as FDA fast-track or breakthrough therapy designations. The majority of the sample (63.6%, 269 / 423) were private companies and the rest were publicly traded companies in the US. About half of companies (53%, 216 / 423) were less than 10 years old, 32% less than 5 years old, and 21% 6-10 years old. Just

over half, (52%, 184/423) had 50 or fewer employees (19% had 1-10, 33% had 11-50). About 23% (72 / 423) of companies reported less than $1M in annual revenue, 38% (118 / 423) $1M and $10M, and 12% (38/ 423) over $100M. About 29.2% (128 / 423) of companies had received FDA expedited program designations, and 11.19% (49 / 423) of them had at least one product approved for use by FDA. See table 2.

Implementation of Cures Act Expanded Access Policy Requirements

Among our study sample, 32.0% (140 /423) of companies had a publicly available expanded access policy. Of these, 31.4% (44 / 140) contained all of the 5 elements described by the Cures Act. Specifically, 82.1% (115 / 140) explained whom to contact at a company with an expanded access request, 72.1% (101 / 140) contained the anticipated time the company takes to acknowledge receipt of an expanded access request, 72.9% (102 / 140) indicated the process for requesting expanded access to a product from the company, 59.7% (83 / 140) included the criteria used by the company for evaluating requests, and 55.1% (76 / 140) linked to or referenced a clinical trial record on ClinicalTrials.gov. Five days was the most common stated response time for acknowledging receipt of an expanded access request (49.4%, 41/83). Most of these policies (82.2%, 115/140) were located on a separate webpage exclusively on expanded access within a company's website. It required at least 2 clicks from a company's landing homepage to reach the expanded access policies for 72.0% (95/140) of companies with policies. About half of the available policies (50.7%, 61/140) followed a structure one of the policy samples posted by the FDA.[7] Lastly, 60% (84/140) of the policies used the term "Expanded Access," but there were wide ranges of other terminologies also used, including "Compassionate Use" (12.9%, 31/140) and "Early Access" (2.1%, 5/140). See table 3.

Company Characteristics Associated with Act Implementation

Companies that were publicly traded (49% vs. 24%; $P < 0.001$), had above the median number of employees (47% vs. 26%; $P < 0.001$), and greater annual revenue (49% vs. 32%; $P = 0.003$) were more likely to have publicly available expanded access policies. In addition, companies that had FDA expedited program designations (59% vs. 21%; $P < 0.001$) and companies that had an FDA-approved product (57% vs. 28%; $P < 0.001$) were more likely to have publicly available expanded access policies. In terms of content posted, older (3.8 vs. 3.0; $P = 0.001$) and larger companies (3.6 vs. 3.2; P

= 0.08) had a higher number of content items described by the Cures Act in their publicly available EA policies on their websites. See table 4.

DISCUSSION

The 21st Century Cures Act requires certain drug companies to have a public policy (for example, on their website) informing patients and physicians about how they can request expanded access to investigational medical products for life-threatening or serious conditions outside of clinical trials. We sought to determine the proportion of applicable companies that have publicly available expanded access policies in accordance with Act requirements, company characteristics (e.g., type, age, size, and revenue) associated with enhanced implementation, and the completeness of publicly available policies.

We found about 1/3 of applicable US based oncology companies have a public expanded access policy as required. However, only about one in three of these public expanded access policies contain all of the informational items described by the Cures Act. For instance, 1 in 5 failed to provide contact information at the company for submitting expanded access requests. Similarly, 2 in 5 policies failed to indicate the criteria the company uses to evaluate expanded access requests. Larger, older, and publicly traded companies with at least one FDA approved drug or FDA expedited program designation were more likely to have a public expanded access policy.

Only two other studies, to our knowledge, have analyzed implementation of Cures Act requirements to have a publicly available EA policy. While our study examined a sample of 423 companies, these prior studies focused on samples of 45 and 100 companies and found that 76% and 47%, respectively, had publicly available expanded access policies.[2,3] Only one of these studies evaluated the completeness of expanded access policies, finding 42% (19) of policies included all five categories of content described in the 21st Century Cures Act. The difference in findings may be due to our inclusion of all applicable US based drug companies, with an oncology product in at least phase 2 development, not just those with an FDA-approved drug, and not just public companies. Our finding on Cures Act implementation rates is more similar to other studies evaluating biopharmaceutical companies' compliance with other US laws governing clinical research, such as clinical trial

registration and results reporting requirements under the US Food and Drug Association Amendments Act (FDAAA).[8–10]

Our findings suggest there may be financial and other resource constraints limiting companies' abilities to develop and publicly disseminate expanded access policies. The findings also suggest that accessing experimental products from smaller and newer companies may be more challenging for patients and clinicians, given these companies are less likely to have publicly available expanded access policies. This finding is consistent with prior articles on expanded access, which described several practical, legal, and ethical challenges associated with implementing expanded access.[11–15] In particular, drug company participation in expanded access may be limited due to administrative burden, as expanded access can require significant human resources.[12] There is a need to improve awareness about processes and procedures for seeking expanded access[16–18] and better enforce Cures Act EA policy requirements. For example, currently, the Act does not appear to specify a penalty for noncompliance. Providing smaller companies with assistance developing expanded access policies through existing initiatives like US FDA Small Business Assistance Programs, may help close information gaps for patient and physician communities on pathways for accessing experimental treatments.[19]

Limitation

We note limitations to our study. First, our analysis relied heavily on hand-collected data. While the advantage of manual data collection regards the uniqueness of data, the disadvantage is that it may not review all available information. For example, the manual search of each website of 423 companies may not capture the entire history of their compliance on expanded access policy. Second, our sample excludes companies headquartered outside the US conducting clinical trials in the US, which can also be subject to the Cures Act, thereby limiting the generalizability of our study results. Third, our study only focused on companies with oncology products, as oncology has traditionally been the most common condition targeted by registered expanded access programs.[4] However, we cannot make claims about non-oncology drug companies. Fourth, because of our data sources and the inclusion of private companies in the sample, market capitalization data were not available for all companies, we thus used company revenue instead. Finally, we equated a publicly available EA policy with a policy being posted on a company's website; it is possible that a company made its

policy public through some other process. In such rare cases, we would have incorrectly considered that company non-compliant due to the lack of policy on its website.

Conclusion

Despite legal requirements, most applicable oncology drug companies do not have public expanded access policies as required. Those policies that are publicly available, are missing important information. These findings suggest there are substantial informational gaps for patients and physicians on how to request non-trial pre-approval access to experimental oncology drugs from certain pharmaceutical companies. These gaps are likely particularly acute for products sponsored by smaller and newer companies. There is significant room for improvement in helping patients and doctors understand and timely navigate access pathways for experimental interventions for serious and life-threatening oncology conditions from individual companies.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

The US Food and Drug Administration (FDA) expanded access pathway allows patients with life-threatening or serious conditions to access investigational drugs outside of trials, under certain conditions. The 21st Century Cures Act ("Cures Act") requires certain drug companies to publicly disclose their expanded access policies, to help support timely medical decisions and close informational gaps for patients and doctors looking to access experimental treatments outside of clinical trials. Only one study to date, to our knowledge, has analyzed implementation of the Cures Act expanded access policy requirements, but it focused on a much narrower company sample generally large companies and those with an FDA-approved drug. Analyzing 45 companies, they found a high implementation rate at 76%.

What question did this study address?

What proportion of applicable US-based oncology companies implement the 21st Century Cures Act requirements for having a publicly available expanded access policy and what company characteristics are associated with implementation?

What does this study add to our knowledge?

Analyzing 423 companies, we found 32% (140/423) had a public expanded access policy and less than 1/3 of the public policies contained all required information (44/14).

How might this change clinical pharmacology or translational science?

These results suggest the Cures Act may be having limited impact on its goals of supporting timely medical decisions and closing informational gaps for patients and doctors looking to access experimental oncology treatments outside of clinical trials, through expanded access, especially for experimental products sponsored by smaller and newer companies.

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AUTHOR CONTRIBUTION

S.K., S.C., J.R., and J.M. wrote the manuscript; S.K. and S.C. designed the research; S.K. performed the research and analyzed the data, and contributed new analytical tools.

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Supplemental File:

1. Supplemental Material

TABLES

Table 1. 21st Century Cures ACT (Section 561 of the Food, Drug, and Cosmetics Act) and corresponding outcome measures used in the study

	Wordings from the Act	**Outcome Measures**
Applicability Condition	i. The first initiation of a phase 2 or phase 3 study (as such terms are defined in section 312.21(b) and (c) of title 21. Code of Federal Regulation (or any successor regulations)) with respect to such investigational drug	
	ii. An applicable, 15 days after the drug receives a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy under subsection (a), (b), or (g), respectively of section 356 of this title	FDA Expedited Programs (Table 2; Table 4)
Content of Policy	Contact information for the manufacturer or distributor to facilitate communication about requests described in subsection (a)	*Policy Content #1* Contact information
	Procedures for making such requests	*Policy Content #2* Request procedures
	The general criteria the manufacturer or distributor will use to evaluate such requests for individual patients, and for responses to such requests	*Policy Content #3* Criteria for evaluating requests
	The length of time the manufacturer or distributor anticipates will be necessary to acknowledge receipt of such requests	*Policy Content #4* Time to acknowledge receipts
	A hyperlink or other reference to the	*Policy Content #5*

	clinical trial record containing information about the expanded access for such drug that is required under section 282(j)(2)(A)(ii)(II)(gg) of title 42	Clinical trial record

Table 2. Characteristics of Study Sample[*]

Characteristics	Study Sample (N = 423)
Disclosure of Expanded Access Policy	
Yes	140 (32.0)
No	298 (68.0)
Company Type	
Public	154 (36.4)
Private	269 (63.6)
Company Age	Median = 14 years
0-5	131 (31.7)
6-10	85 (20.9)
11-15	77 (18.6)
16-20	42 (10.2)
21-25	17 (4.1)
26+	61 (14.8)
Number of Employees	Median = 50 employees
1-10	66 (18.7)
11-50	118 (33.4)
51-100	53 (15.0)
101-250	53 (15.0)
251-500	21 (6.0)
501-1000	15 (4.3)
1001-5000	8 (2.3)
5001-10000	5 (1.4)
10001+	14 (4.0)
Annual Revenue	Median = $10M in annual revenue
Less than $1M	72 (23.2)
$1M to $10M	118 (38.1)
$10M to $50M	69 (22.3)
$50M to $100M	12 (3.9)
$100M to $500M	20 (6.5)
$500M to $1B	3 (1.0)
$1B to $10B	12 (3.9)
$10B+	3 (1.0)
FDA Expedited Programs	

[*] Percentages may not total 100 because for each data there is minority of drug companies with missing data.

Yes	128 (29.2)
No	310 (70.8)
FDA Approved	
Yes	49 (11.19)
No	389 (88.81)

Table 3. Main Outcome Measure[*]

Characteristics	**Study Sample (N = 423)**
Disclosure of Expanded Access Policy	
Yes	140 (32.0)
No	298 (68.0)
	Expanded Access Policies (N = 140)
Policy Content	
1 Contact information	115 (82.1)
2 Request procedures	101 (72.1)
3 Criteria for evaluating requests	102 (72.9)
4 Time to acknowledge receipts	83 (59.7)
5 Clinical trial record	76 (55.1)
All	44 (31.4)
Response Time	
1 Day	8 (9.6)
2 Days	12 (14.5)
3 Days	2 (2.4)
5 Days	41 (49.4)
6 – 10 Days	14 (16.9)
11+ Days	6 (7.2)
Separate Webpage	
Yes	115 (82.1)
No	25 (17.9)
Number of Clicks	
1	22 (16.7)
2	95 (72.0)
3	15 (11.4)
Expanded Access Policy Sample	
1	9 (6.4)
2	60 (42.9)
3	2 (1.4)
Others	68 (48.6)
Expanded Access Terminology Used	
"Access (to investigational drugs)"	11 (4.6)
"Compassionate Use"	31 (12.9)

[*] Percentages may not total 100 because for each data there is minority of drug companies with missing data.

"Early Access"	5 (2.1)
"Expanded Access"	84 (60)
Combinations of above terms	18 (7.6)
Others ("Managed Access", "Early Patient Access", "Patient's Access"	30 (12.6)

Table 4. Comparison of Compliance based on the Company Characteristics

	Outcome Measure	Group A	Group B	Difference (95% CI)	P-Value
Company Type		**Public**	**Private**		
	Policy Disclosure (Yes or No)	0.49	0.24	0.26 (0.16 to 0.35)	0.00
	Policy Contents Posted (n/5)	3.55	3.26	0.28 (-0.24 to 0.80)	0.14
		Above Median	**Below Median**		
Company Age	Policy Disclosure (Yes or No)	0.30	0.34	-0.04 (-0.05 to 0.13)	0.19
	Policy Contents Posted (n/5)	3.84	2.97	0.87 (-0.37 to 1.37)	0.00
Number of Employees	Policy Disclosure (Yes or No)	0.47	0.26	0.21 (0.11 to 0.31)	0.00
	Policy Contents Posted (n/5)	3.61	3.20	0.41 (-0.17 to 0.99)	0.08
Annual Revenue	Policy Disclosure (Yes or No)	0.49	0.32	0.17 (0.06 to 0.28)	0.00
	Policy Contents Posted (n/5)	3.48	3.44	0.04 (-0.52 to 0.60)	0.44
		Yes	**No**		
FDA Expedited Programs	Policy Disclosure (Yes or No)	0.59	0.21	0.38 (0.28 to 0.47)	0.00
	Policy Contents Posted (n/5)	3.62	3.21	0.40 (-0.11 to 0.92)	0.12
FDA Approved	Policy Disclosure (Yes or No)	0.57	0.28	0.28 (0.13 to 0.43)	0.00