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Time to inclusion in clinical guidance documents for non-oncological orphan drugs and biologics with expedited FDA designations: a retrospective survival analysis

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ABSTRACT

Objectives Drug and biological products that treat rare, serious or life-threatening conditions can receive US Food and Drug Administration (FDA) orphan designation and expedited programme designations (accelerated approval, breakthrough therapy, fast track or priority review) meant to incentivise development. Timely recommendations from guidance documents may encourage more rapid and appropriate use and access to these medicines for serious conditions. We sought to determine time between FDA approval and inclusion in guidance documents for non-oncological orphan products overall and by number and type of expedited programme designations.

Design and setting Retrospective survival analysis of non-oncological orphan products with ≥1 expedited designation approved since 1992. In June 2020, PubMed, Turning Research into Practice and Guideline Central databases were searched to identify guidance documents influencing US practice that included each product.

Main outcomes and measures The primary outcome was time to guidance inclusion, defined as any recommendation on use provided within the recommendation framework used by the guidance document.

Results Among 135 included non-oncological orphan products, 97.0% (n=131) were designated with priority review, 49.6% (n=67) fast track, 16.3% (n=22) breakthrough therapy and 14.1% (n=19) accelerated approval. Sixty per cent of products (n=81) received ≥2 designations. Overall, 74.1% (n=100) were included in a guidance document. The median time to inclusion was 2.87 years (IQR 2.21–4.18) for the entire cohort. In survival analyses, guidance inclusion was more likely to occur earlier for products with ≥2 designations (HR, 1.84; 95% CI 1.21 to 2.79) and for those with fast-track designation compared with priority review (HR 1.40; 95% CI 1.02 to 2.0). Of 35 products not included in a guidance document, 54.3% (n=19) were approved in 2018 or later.

Conclusions Among non-oncological orphan products with priority designations, nearly 3 years had passed between FDA approval and inclusion in any guidance document. These findings suggest that despite efforts to expedite availability, appropriate access to these treatments may be delayed because of the lack of timely guidance on their use in clinical practice.

Strengths and limitations of this study

► This study evaluated Food and Drug Administration-approved non-oncological drug and biological products with orphan and expedited designations, representing a subset of therapies that fulfil unmet medical needs.
► This study evaluated the time between product approval and inclusion of the product in relevant clinical practice guidance documents, which were identified with a systematic literature search and author screening and review.
► The study excluded non-oncological products as well as non-orphan products, which limits generalisability of findings.
► The most recently approved products may not have been approved for periods of time that were sufficient to warrant guidance updates.

INTRODUCTION

Drugs that treat rare, serious or life-threatening diseases can present challenges in development and access. To provide manufacturers incentives to develop such drugs when otherwise few exist, regulatory programmes were created, including the Orphan Drug Act (ODA) of 1983 and the US Food and Drug Administration (FDA) expedited programmes.[1 2]

The ODA provides financial incentives, including research tax credits, access to grants, and 7-year exclusivity, to encourage development of drugs for diseases affecting fewer than 200 000 patients of a specified population or subset (eg, paediatric patients) of a population.[1 3 4] Expedited programmes facilitate and expedite development and FDA review of drugs that address unmet medical needs of serious or life-threatening conditions to help ensure these therapies are quickly approved and available to patients

Table 1	Food and Drug Administration (FDA) expedited pathways[2]
Expedited programme	**Programme descriptions**
Accelerated approval	Allows products for serious conditions that fill an unmet medical need to be approved based on a surrogate or intermediate clinical endpoint
Breakthrough therapy	Designed to expedite the development and review of products intended to treat a serious condition which may demonstrate substantial improvement over alternative available therapy
Fast-track designation	Designed to facilitate the development and expedite the review of products to treat serious conditions and fill an unmet medical need
Priority review	Designation can be applied for products that, if approved, would be significant improvements in the safety or effectiveness of treatment, diagnosis or prevention of serious conditions, and implements a goal for FDA to take action on a product application within 6 months, compared with 10 months under standard review

once it is clear that their benefits justify their risks.[2] Expedited programmes include fast track, breakthrough therapy, accelerated approval and priority review designations (table 1).[2]

The ODA and expedited programmes have been widely and increasingly used. Since 1987, the number of expedited programmes granted to new drugs has increased by 2.6% annually.[5] In 2019, 60% of novel product approvals received at least one of the four expedited programme designations.[6] Further, orphan drugs or biologics composed 43% of all novel product approvals between 2012 and 2019.[5] Between the time of the passage of the ODA in 1983 and 2017, 575 drug and biological products for rare diseases have been developed, providing novel therapeutic options for rare diseases.[3] Orphan drugs also have an outsized impact on spending, with increases between 4% and 10% of total prescription drug spending between 1997 and 2017.[7] In 2018, orphan drug sales account for approximately 30% of the US$170 billion in sales generated from drugs approved between 2010 and 2019.[8] While similar spending data are unavailable for products with expedited programme designations, these products are also typically costly.

While the ODA and expedited programmes encourage market availability, they do not ensure appropriate patient access. For example, Chambers *et al* reported in a 2019 analysis that the frequency of restrictions for orphan drugs was 30% overall, and varied from 11% to 65% across 17 of the largest 20 US private health plans.[9] Importantly, this analysis found that only 16% of 302 drug-indication pairs were covered the same way by all health plans. Using the same data, Chambers *et al* later reported that orphan drugs with expedited approval were approximately 30% more likely than those without expedited approval to have coverage restrictions.[10] Another analysis reported that approximately one-quarter of indications for drugs with orphan or expedited designations had restrictions on use.[11] Challenges in covering drugs with expedited designations have also been documented; these include lack of coverage for some drugs approved with expedited designations among private payers because of high cost and, consistent with the lower evidentiary standards of some designations, a lack of evidence.[12]

The increasing prevalence, high cost and limited evidence for drugs approved with orphan and expedited designations present challenges in determining appropriate coverage decisions. Not surprisingly, clinical data were found to be the most important factor driving benefit design for orphan drugs in a survey of commercial and public payers.[13] However, studies have documented the low quality of preapproval and postapproval studies of drugs approved with orphan or expedited designations, including infrequent use of randomization, blinding and terminal clinical endpoints.[14–16] These studies did not report whether coverage decisions for orphan drugs were justified and consistent with evidence-based practice; such analyses could be facilitated by recommendations from guidance documents.

Experts have also described the disconnect between the cost of orphan drugs and their clinical benefit, threatening the sustainability of healthcare systems.[17 18] For example, the costs per quality-adjusted life-year were estimated in 2015 to be US$640 000 and US$3.6 million for ivacaftor and ivacaftor/lumacaftor, respectively, two agents approved by FDA for the treatment of patients with cystic fibrosis and specific genetic mutations.[19] Globally, approximately 2600 and 25 000 patients, respectively, carried mutations that made them eligible for these agents. To address this issue, innovative pricing strategies have been proposed, including some that discount early market prices of orphan drugs while the evidence base is immature, and adjust prices according to subsequent research and use.[3 18] The allocation of scarce resources to high-cost orphan drugs presents a challenge of balancing the health of a population with that of a small subgroup of people with orphan diseases.[20] Some have suggested using higher cost-effectiveness thresholds or weighted cost-effectiveness ratios for orphan diseases to ensure these patients retain access to care. Nonetheless, these strategies are not widely applied, and would be challenging to implement during the early stages of availability of orphan drugs when evidence is limited.[17 20]

Confronted with these challenges, formal evidence-based recommendations from clinical practice guidances may assist policy-makers in coverage determinations for drugs with orphan and expedited designations in ways

that balance cost, access and utility. The Institute of Medicine (IOM) states that clinical practice guidelines provide a systematic aid to making complex medical decisions, combining scientific evidence, clinicians' experience and patient values, to improve health outcomes.[21] Indeed, a review of international pricing strategies and coverage of orphan drugs and personalised medicine found that clinical practice guidelines strongly influence payer decisions.[22] While individual clinicians lack the resources to perform comprehensive reviews of evidence from patient, payer and public health perspectives, guideline panels do possess these resources and provide additional clinical insight from expert leaders in practice areas specific to the guideline.[23] Moreover, some guideline development processes, such as Grading of Recommendations, Assessment, Development, and Evaluation (GRADE), provide recommendations in a framework that has policy-level implications. Such recommendations could facilitate coverage decisions and promote appropriate access. Therefore, we sought to evaluate the time to inclusion in clinical practice guidance documents for drug and biological products approved with orphan and expedited designations.

METHODS

Data sources

We used publicly available data from FDA Center for Drug Evaluation and Research of New Molecular Entity Drug and New Biologic Approvals.[24] This dataset includes regulatory and product information for products approved from 1985 through 2019, including dates of approval, types of approval and approved indications, that were current as of 21 February 2020 at the time of data collection.

Inclusion and exclusion criteria

Products were included that were approved via a New Drug Application or Biologic License Application, granted orphan drug designation and granted 1 or more of the following expedited programme designations: fast track, accelerated approval, breakthrough therapy and priority review. The earliest available of these programmes (priority review) was instituted in 1992; thus, we excluded products approved prior to this year. Products were included regardless of brand or generic status. Products that were addressed in guidances prior to their FDA approval were excluded from analyses, as these would not have been at risk for guidance inclusion at the time of their approval.

We considered the potential for individual products to be approved for more than 1 indication, and the possibility that information supporting the first approval may influence the decision for guideline panels to act on information from a second approval. Therefore, we planned to analyse only the first approved indication of a drug should this situation occur.

The major guidance documents for oncology indications in the USA are produced by the National Comprehensive Cancer Network (NCCN); these are not indexed in publicly searchable databases (eg, PubMed), nor are historical documents available in archived format at the NCCN website. This precludes the ability to identify historical and contemporaneous guidances that were published at the time of earlier product approvals. Therefore, we excluded products approved for oncology indications.

Identification of guidance documents

We searched for guidance documents (including full guidelines as well as focused updates and similar documents) influencing US practice that were applicable to each product's approved indication in order to determine the time to first inclusion in a guidance document. Our systematic search strategy intended to identify the most contemporaneous guidance documents following each product's approval. To achieve this, we searched PubMed, which would provide a comprehensive historical database of publications. We searched, as secondary resources, the Turning Research into Practice database and Guideline Central. These guideline repositories were prioritised after PubMed because they often remove outdated guidances, preventing our ability to identify contemporaneous documents.

Our PubMed search strategy involved appending a customised search string with terms for each product indication to a standardised search string including a filter for identifying guidance documents (online supplemental file 1) and a filter for a time period applicable to each product approval. This time period filter included a 6-month lookback period prior to the product's approval (to capture any guidances made in anticipation of a product's impending approval) and continued until 30 June 2020. The customised search string for each product indication was created and reviewed by at least two authors. Candidate publications were collected and reviewed.

Outcome measures

The outcome of interest was the time to first clinical recommendation for a product in guidance documents from organisations influencing US practice, which we considered as any recommendation for or against clinical use or a statement that evidence is insufficient to make a recommendation as performed within the recommendation framework used by the guidance document (eg, GRADE). When available, we recorded this information and calculated the time between product approval and publication date for the first inclusion in a guidance document. Products with no applicable guidance document or no inclusion in a guidance document by the time of our search were considered censored.

Analysis

We calculated median times to guidance document inclusion overall and for each separate expedited programme designation. Kaplan-Meier survival curves were prepared

Table 2 Characteristics of non-oncology orphan drugs and biologics approved with expedited designations

Product characteristics	All products (n=136)
Application type, n (%)	
NDA	95 (69.9)
BLA	41 (30.1)
Expedited pathway, n (%)	
Priority review	131 (96.3)
Accelerated approval	19 (14.0)
Breakthrough therapy	22 (16.2)
Fast track	68 (50.0)
Total designations granted, n (%)	
1	55 (40.4)
2	59 (43.4)
3	21 (15.4)
4	1 (0.7)

BLA, Biologics License Application; NDA, New Drug Application.

Table 3 Inclusion in clinical guidance documents for non-oncology orphan drugs and biologics approved with expedited designations

Addressed in guidance document		
Overall cohort, n (%)		101 (74.3)
Priority review		96 (73.3)
Accelerated approval		15 (78.9)
Breakthrough therapy		11 (50.0)
Fast track		51 (75.0)
	Years to guidance inclusion, median (IQR)	HR (95% CI)
Overall cohort	2.84 (2.18, 4.18)	–
Accelerated approval	2.18 (1.68, 13.49)	1.3 (0.75 to 2.2)
Breakthrough therapy	2.55 (1.58, NE)	1.3 (0.71 to 2.5)
Fast track	2.18 (1.68, 3.74)	1.4 (1.02 to 2.0)
Priority review	2.87 (2.55, 4.71)	Ref
Number of designations		
≥2	2.21 (1.97, 2.88)	1.78 (1.18 to 2.69)
1	4.18 (3.44, 7.79)	Ref

NE, not estimable.

and compared using the log-rank test. Descriptive statistics were calculated using proportions and mean (SD) or median (IQR), as appropriate.

We performed Cox proportional hazards modelling to compute HRs for the time to guidance document inclusion for products granted 2 or more expedited programme designations versus only 1, and for products approved with fast track, accelerated approval and breakthrough therapy designations (which permit a lower evidentiary standard) versus priority review designation (which does not modify the evidentiary standard).

Patient and public involvement
No patients were involved in the development of the research question or design of the study.

RESULTS
The FDA approved 917 new drug or biological products from 1992 through December 2019, of which 284 (30.9%) were approved for at least 1 orphan disease.[24] Eight products were addressed in a guideline before approval and were excluded from analyses. Overall, 136 non-oncology products received orphan designation and were included in the analysis. Of these, 96.3% (n=131) were designated with priority review, 50.0% (n=68) fast track, 16.2% (n=22) breakthrough therapy and 14.0% (n=19) accelerated approval (table 2). Two or more expedited designations were received by 59.5% (n=81) of products.

Overall, 74.3% of products (n=101) were addressed in a guidance document (table 3). The median time to guidance inclusion was 2.84 years (IQR 2.18–4.18) for the entire cohort, and did not significantly differ overall across expedited programme designations (log-rank p=0.21; figure 1). However, compared with products with 1 programme designation, guidance inclusion was more

likely to occur earlier for products with ≥2 designations compared with those with 1 designation (median, 2.21 vs 4.18 years, respectively; Cox proportional HR, 1.78; 95% CI 1.18 to 2.69; figure 2). Compared with products approved with priority review, only those with fast-track
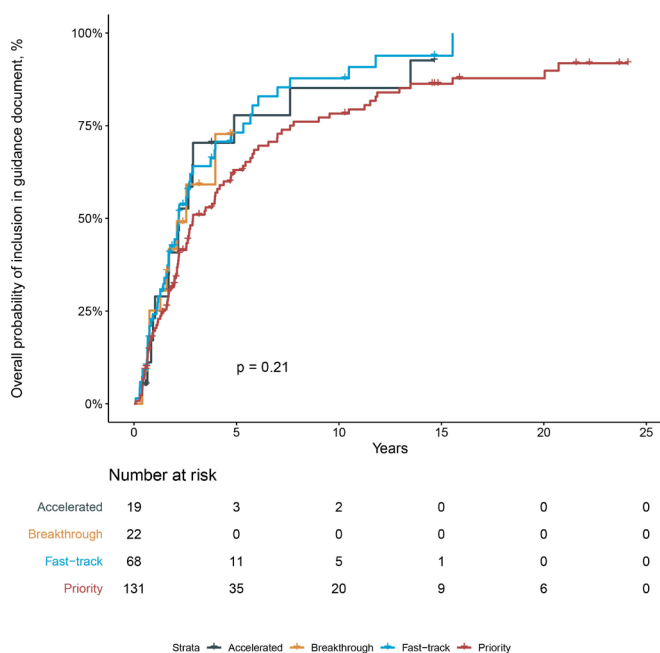

Number at risk					
Accelerated	19	3	2	0	0	0
Breakthrough	22	0	0	0	0	0
Fast-track	68	11	5	1	0	0
Priority	131	35	20	9	6	0

Figure 1 Kaplan-Meier plot of inclusion in guidance documents for orphan products approved via expedited pathways.

Number at risk

1 designation	55	23	14	8	6	0
≥2 designations	81	12	6	1	0	0

Strata — 1 designation — ≥2 designations

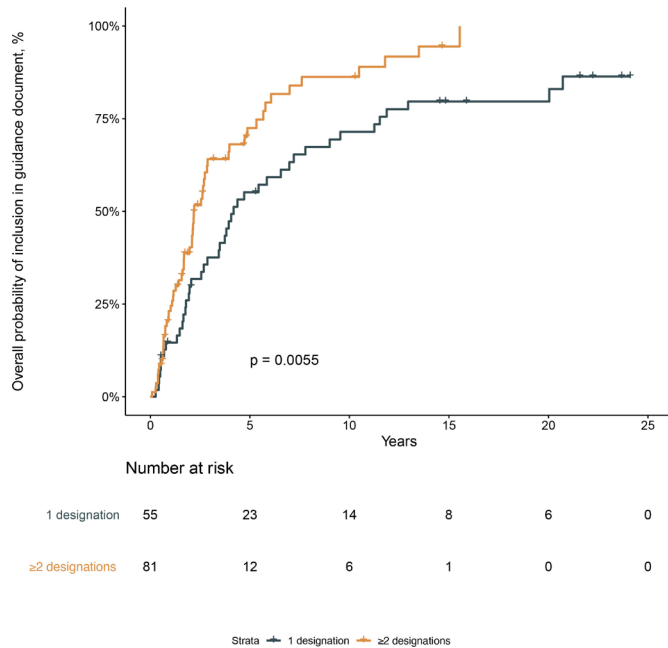**Figure 2** Kaplan-Meier plot of inclusion in guidance documents for orphan products approved with 1 or ≥2 expedited designations.

Table 4 Characteristics of non-oncology orphan drugs and biologics not included in guidance documents

Product characteristics	All products (n=136)
Total NDA and BLA approvals, n (%)	35
NDA	27 (77.1)
BLA	8 (22.9)
Expedited pathway, n (%)	
Priority review	35 (100.0)
Accelerated approval	4 (11.4)
Breakthrough therapy	11 (31.4)
Fast track	17 (48.6)
Total designations granted, n (%)	
1	12 (34.3)
2	15 (42.9)
3	7 (20.0)
4	1 (2.9)
Approval year, n (%)	
1996	2 (5.7)
1998	2 (5.7)
2004	2 (5.7)
2005	3 (8.6)
2010	1 (2.9)
2015	3 (8.6)
2016	1 (2.9)
2017	2 (5.7)
2018	8 (22.9)
2019	11 (31.4)
Years since approval, median (IQR)	2.20 (1.13, 12.42)

BLA, Biologics License Application; NDA, New Drug Application.

designation were more likely to be included earlier in guidance documents (HR, 1.40; 95% CI 1.02 to 2.0).

Of 35 products not included in a guidance document, 54.3% (n=19) were approved in 2018 or later (table 4); other characteristics were similar to those of products included in a guidance document. A majority of these products received either priority review designation alone (n=35) or both priority review and fast-track designations (n=32).

DISCUSSION
To our knowledge, this is the first study to describe time between approval of orphan products with expedited designations and their inclusion in clinical practice guidance documents. These findings have importance in the current regulatory environment. The annual number of orphan drug designations assigned by FDA has increased from roughly 60 in 2002 to 427 in 2017.[1] Additionally, the mean annual growth rate of orphan products has been predicted to increase by 11.1% between 2017 and 2022, significantly higher than that predicted for non-orphan products (5.3%).

The roughly 3-year period for guidance inclusion could be due, in part, to the resource investment demanded by rigorous guideline development.[21] The mobilisation of key stakeholders and contributors can be a lengthy process. However, it can be streamlined; for example, NCCN guidelines provide in-depth, transparent methods for guideline development and committee mobilisation.[25] The NCCN guidance documents are updated at least annually and often in response to new product approvals. This facilitates timely decision-making and can serve as

a model for other guideline panels. Other explanations for the delay between approval and guidance provision may relate to the limited evidence available at the time of product approval. Recommendations for use of orphan drugs should be supported by robust evidence; such evidence may not be immediately available, and professional societies may deem full guidance production or revision unjustified. Nonetheless, statements regarding the limited evidence and recommendations for restricted, yet appropriate, use can still be useful to policy-makers in justifying coverage decisions.

We also found that orphan products with 2 or more expedited designations were included more quickly into guidance documents compared with those with fewer designations. This may suggest that societies recognise an additive effect of multiple designations. However, we found limited differences between expedited designations; therefore, it is unclear how the quality rather than quantity of expedited designations may influence the time to guidance document inclusion.

The IOM provides recommendations on updating guidelines in *Clinical Practice Guidelines We Can Trust.*[21] The IOM states that literature should be monitored regularly to identify new and relevant evidence, and guidance should be updated when evidence suggests need for modification of a clinically important recommendation. Guidance revision may be needed when a recommended intervention causes previously unknown harm, and when a recommendation applies to new populations. The first of these situations is reflected in findings by Mostaghim *et al* which identified a 38% increased rate of safety-related label changes for products approved via expedited pathways.[26] The second is represented by the fact that orphan products are by nature the first treatments available for a population. To optimise market entry of new medications, Godman *et al* in a review of access barriers to new medicines, suggested postmarketing evaluation of prescribing practices against current guidelines.[27] Thus, approval of products such as those in our analysis could prompt initiation or revision of guidance documents.

The availability of clinical recommendations from professional societies could be considered along with other factors in broader policy and formulary deliberations related to orphan drugs. For example, multicriteria decision analysis (MCDA) is an explicit framework used to evaluate the utility of health technologies to determine whether they merit funding.[17 28] Approaches using MCDA incorporate weighted scores for various criteria to generate a composite score that facilitates comparison of health technologies. Criteria considered in MCDA may include clinical benefit and safety, quality of evidence, implementation feasibility, innovation, clinical need and societal and ethical values.[28] The availability of recommendations from respected professional societies might play a supporting role in MCDA.

Several products in this analysis serve as useful examples of rapid and delayed inclusion in guidance documents. For example, pirfenidone, a treatment for idiopathic pulmonary fibrosis that received priority review, breakthrough therapy, and fast-track designations, was included in an international guideline 8 months after its approval.[29] The publication of new evidence was a predefined surveillance criterion for updates according to the previous version of the guideline.

In contrast, eteplirsen, approved for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed mutation amenable to exon 51 skipping, has yet to be addressed in guidance documents.[24] Eteplirsen received priority review, accelerated approval, and fast-track designations, and was approved in September 2016 based on a trial including 12 children that evaluated the surrogate outcome of increased dystrophin in skeletal muscle.[30–32] Many insurers declined coverage or imposed restrictions on use of eteplirsen due, at least in part, to this limited evidence.[30 33] Advocacy groups and parents disputed coverage decisions because of its high cost.[33] While various factors contributed to the uncertain value of eteplirsen, earlier guidance from professional societies may have alleviated some of these challenges. Since the approval of eteplirsen, 3 additional antisense oligonucleotides have been approved to treat DMD.[34–36] To date, these therapies have not been addressed in guidance documents.

There are challenges to providing recommendations for use of products in this analysis. Orphan diseases are less likely to be represented by a professional organisation equipped to develop a clinical practice guideline.[21] Additionally, orphan drug approvals are often based on clinical studies with less rigorous designs or results based on surrogate endpoints. With limited evidence presented at approval for some orphan products, the role of expert opinion in guideline development may be outsized compared with its role in non-orphan products.

Our study has several limitations. First, the development of search strings and manual screening present risk of subjectivity in identifying relevant documents. However, we attempted to mitigate this through review of each search string by at least two authors and secondary review of selected documents. Second, oncological products were excluded from our search strategy because of the inability to retrieve historic guidelines from NCCN, a primary guidance for oncology practice in the USA. This prohibits generalisability to oncology products. Additionally, we restricted our analysis to products with both orphan and expedited designations, limiting generalisability to non-orphan products. Finally, our analyses identified that the median time to guidance inclusion was almost 3 years. Thus, products approved in recent years may have not had sufficient time to be included in guidances at the time of data collection. However, specific cases, such as that of pirfenidone, suggest that a strategic approach could promote more rapid inclusion of recent approvals in guidance documents.

In conclusion, we found that for FDA-approved orphan products with expedited programme designations, approximately 3 years elapsed between product approval and inclusion in guidance documents; guidance inclusion was more likely to occur earlier for products with ≥2 versus those with 1 designation, and for those with fast-track versus priority review designation. More timely development of guidance documents after approval of these products could encourage more rapid and appropriate uptake into practice and could be initiated when FDA approval is anticipated. Further research is needed to better characterise barriers to inclusion of these products in guidance documents and subsequently, their appropriate use and access.

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