WHITE PAPER

AMCP PARTNERSHIP FORUM:

ADDRESSING EVIDENCE GAPS IN THE FDA ACCELERATED APPROVAL: PAYER PERSPECTIVES

Abstract

To support balancing patient access with payer needs related to the U.S. Food and Drug Administration (FDA) Accelerated Approval (AA) pathway program, AMCP held a multistakeholder Partnership Forum in Alexandria, VA, November 18–19, 2021. The group of 35 experts included representatives from health plans, pharmacy benefit managers, integrated delivery systems, patient advocacy organizations, research and policy organizations, academia, and biopharmaceutical manufacturers. These participants were asked to: 1) identify gaps between FDA AA requirements and treatment outcomes valued by payers, 2) explore opportunities for an evidence ecosystem to address these gaps, and 3) evaluate and prioritize policy options to facilitate communication of payer needs, reduce financial uncertainty, or improve the time between FDA approval or clearance and payer coverage decisions. Participants in this forum felt it was important to continue to support innovation in drug development and patient access through the FDA expedited programs while also recognizing payer needs to aid coverage determinations and increase stakeholder trust in the AA review process program. Specifically, more robust clinical trial evidence and correlating surrogate endpoints with meaningful outcomes and developing an evidence ecosystem to deliver information more readily were seen as key. To note the various potential policy solutions reviewed, policies incentivizing the completion of confirmatory trials garnered the most interest and was thought to have the potential for the most impact.

Introduction

In the late 1980s, the public health crisis associated with human immunodeficiency virus (HIV) and autoimmune deficiency syndrome (AIDS) spurred Congress to pass legislation to speed development of new treatments.[1] This initially led to the codification into law of the Fast Track designation, and subsequent legislation created three additional programs allowing the FDA to expedite drug approvals.[1] The aim of these programs has been to increase timely patient access to medications that address an unmet medical need in the treatment of a serious or life-threatening condition.[1] Over the past quarter century, they have been widely used, applying to nearly 75% of novel FDA-approved drug indications in 2021.[2]

In each of the Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval (AA) programs, the features differ (Table 1).[3] Three of the programs expedite the new drug application review time at the FDA, make possible additional guidance for manufacturers, or provide incentives for drug development.[3] Only the AA pathway, however, alters evidentiary requirements and allows approval based on a surrogate or an intermediate clinical endpoint.[3] Studies using these surrogate or intermediate endpoints must still be "adequate and well-controlled" as with those using true clinical outcomes, but confirmatory trials must also be completed after FDA approval.[1,3] The product label may then be revised, or the product indication may be withdrawn if clinical benefit is not verified.[1,3]

Even outcomes that serve as the basis for traditional regulatory approval may diverge from payer evidence requirements; therefore, the use of surrogate endpoints adds another layer of complexity to the drug evaluation process.[4–6] Traditional clinical endpoints for FDA approval, for instance, "…measure whether people in a trial feel or function better or live longer" based on symptom relief, morbidity, or mortality.[7] Endpoints for AA need only

be "…reasonably likely to predict a real clinical benefit."[3,7] According to internal AMCP research, payers with fiduciary responsibility desire information on product effectiveness, safety, medical cost offsets, and other economic endpoints.

Consider the example of sickle cell disease to exemplify these differences. Patient-reported pain and end-organ damage are traditionally used as clinical endpoints, and lab-based hemoglobin changes (a proxy for pain) are recognized by the FDA as an acceptable surrogate endpoint.[8] In contrast, payers desire data on pain medication use, emergency room visits, and total cost of care.[9] This can create confusion among providers and patients because without adequate evidence, FDA approval may not guarantee payer coverage.

Despite nearly three decades of experience with these programs, tension with accelerating development to expedite access to some treatments continues. From one perspective, patient groups advocate expansion of FDA regulatory flexibility for incurable conditions.[10–13] In parallel, the U.S. Department of Health and Human Services (HHS) Office of Inspector General and the FDA have proposed reforms in the FDA approval processes.[14-16] These include changes to product evaluation and indication withdrawal, legislative proposals to ensure timely evidence development, and alterations to internal processes.[14–16] Other organizations have put forth policy and reimbursement proposals to address the uncertainty associated with medications approved under the AA pathway but retain the benefits achieved.[17–19]

To support balancing patient access with payer needs related to AA, AMCP held a multistakeholder Partnership Forum in Alexandria, VA, November 18–19, 2021. The group of 35 experts included representatives from health plans, pharmacy benefit managers, integrated delivery systems, patient advocacy organizations, research and policy organizations, academia, and biopharmaceutical manufacturers. These participants were asked to (1) identify gaps between FDA AA requirements and treatment outcomes valued by payers, (2) explore opportunities for an evidence ecosystem to address these gaps, and (3) evaluate and prioritize policy options to facilitate communication of payer needs, reduce financial uncertainty, or improve the time between FDA approval or clearance and payer coverage decisions. To accomplish this, participants reviewed findings from a pre-forum survey of health care decision makers conducted by the AMCP Foundation, reviewed regulatory terminology, engaged in panel sessions, and participated in breakout groups.

Breakout groups evaluated four hypothetical case studies to identify the gaps between various evidentiary requirements and explore opportunities for evidence to address those gaps. These case studies were modeled on existing medications representative of certain characteristics including population treated (pediatric vs adult), prevalence (rare vs common), and clinical condition (oncology vs non-oncology). Groups also evaluated seven potential policy solutions and described their anticipated impact on patient access, financial uncertainty, and incentives for innovation. These proceedings synthesize forum outcomes based on transcripts from the speaker presentations, panel discussions, and breakout summaries; however, the findings should not be construed as consensus or the perspective of any individual participant organization. Key themes emerged and are described below.

Expedite Innovation but Balance with Meaningful Outcomes for Coverage Determinations

Partnership forum participant perceptions of the need for AA to expedite innovation varied. One representative from a patient organization explained these programs offer hope to the families of patients with rare pediatric conditions. Also referenced was that research demonstrated drugs cleared through these expedited programs have typically offered greater benefits than drugs approved by traditional programs.[20] Nevertheless, only one in three health care decision makers in the pre-forum survey rated the AA program as either "very" or "extremely necessary."[21]

One of the key challenges with AA identified by participants related to the evidence review process for determining payer coverage. Of primary concern, is that the evidence available at product launch is often limited to small, single-arm studies using surrogate or intermediate endpoints with uncertain meaning. It was noted by a payer participant attending the partnership forum, the evidence available requires "…a leap of faith. There are some leaps the size of a crack in the sidewalk, some the size of the Grand Canyon, and most are somewhere in between. How willing are you to jump depends on the urgency of the situation."

Additionally, participants stated that review by the payers of the products approved through the AA pathway is often distinctive compared to traditionally approved products. In the pre-forum survey for example, 30% of all payer respondents reported having a separate review process for therapies receiving AA.[21] And those at the forum also expressed the need for subsequent re-review of these products when new evidence became available or if confirmatory trials remained incomplete after a certain period, meaning that a process for monitoring them needs to be in place.

Most participants recommended adaptations or augmentation of existing Pharmacy & Therapeutics review processes to identify and more easily update formularies and coverage policies. However, they cautioned that AA does not ensure accelerated reimbursement by coverage entities even with a payer's enhanced evaluation processes.

Clarify Terminology and Requirements that Serve as the Basis for Accelerated Approval

Participants emphasized the need to clarify the existing regulatory framework including terminology and requirements that serve as the basis for accelerated approvals. Without this, they noted, evidence review is challenging and may result in a treatment not being covered, a medical use policy being delayed, or coverage determinations needing to be made on a patient-by-patient basis.

For instance, the AA pathway was "…designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need."[3] The FDA offers examples of serious conditions, such as AIDS, Alzheimer's disease, heart failure, and cancers; however, they do not provide a clear definition. For filling

an unmet need, they also offer as additional explanation that the therapy must provide a treatment where one does not exist or offers benefits over existing treatments.[1,3] However, payer participants observed uncertainty often exists regarding the clinical course of disease or which outcomes matter to patients, providers and payers especially for rare conditions and, therefore, understanding the unmet need can be difficult.

Participants indicated payers are also seeking evidence from more rigorous clinical trials than what may initially be available for AA medications, which they felt is best accomplished through confirmatory trial completion after FDA approval. This includes larger, randomized, active-comparator trials that ideally demonstrate appreciable treatment differences between the new drug and placebo or comparator, and among subpopulations.

Correlate Surrogate Endpoints with Meaningful Outcomes

Forum participants underscored the need to correlate surrogate endpoints with meaningful clinical outcomes to increase payer confidence in the treatment effects of medications in which they are used for FDA approval. Surrogate and intermediate clinical endpoints can serve as the basis for FDA approval or licensure of a medication through the AA pathway based on five criteria (causality, biological plausibility, specificity, proportionality, universality) and FDA consideration of risk-benefit.[1,22] Even though they must be likely to provide clinical benefit, they are not true clinical outcome endpoints. This poses a challenge as shown in the pre-forum survey where 38% of all payer decision makers reported being "not at all" or "not very confident" in applying surrogate endpoint data to formulary decisions.[21]

According to participants, gaps in knowledge associated with many surrogate endpoints include understanding the role of the surrogate endpoint in the condition's pathophysiology, the measurement tool or scale used to assess it (including its properties and what is considered a clinically meaningful change), and the expected timeframe for a clinically meaningful change to occur. This information is important especially for rare conditions with unknown or not well-understood endpoints, or no commonly accepted clinical access tools as exemplified in one case study, for example, which used the Unified Parkinson's Disease Rating Scale and other motor scales relatively unfamiliar to many participants.

In addition to clinical endpoints, participants also expressed an increasing need for information on the economic implications of AA medications to enable the assessment of their value. As one forum participant noted, in the early 1990s, most products approved through the AA pathway were fewer than 100,000 dollars. Today, many have six- or seven-figure prices. Therefore, the ability to correlate surrogate outcomes with financial and budget impact data (e.g., number of patients needed to treat, expected medical cost offsets, and the time to achieve these) were considered critical elements.

Physician Specialists, patient groups, and biopharmaceutical company medical experts were suggested by participants to aid in the understanding of specific surrogate endpoints and the correlation to meaningful outcomes. Some payer participants seek input from specialists during the evidence review process to achieve this. Patient advocacy participants confirmed that patient communities, especially those with rare diseases, have long established longitudinal patient registries and can help payers and health care providers understand relevant surro-

gate endpoints and what patients consider their unmet needs. Also, several participants highlighted the role of pre-approval information exchange and the AMCP Format for Formulary Submissions guidance for unapproved product dossiers.[23]

Bridge Evidence Gaps by Building an Evidence Ecosystem

Key evidence needs related to AA medications identified by participants were (1) more robust data clearly delineating the role of the medication at approval and (2) data that allow assessment of long-term safety, efficacy, and durability of effect. Forum participants discussed the importance of building an evidence ecosystem with enhanced data and analytic capabilities to better manage evidence gaps. This evidence ecosystem would systematically collect data, for instance, from supplemental data sources like electronic health records, patient registries, and other post-marketing channels. It could also include wider access to and leverage of the FDA Sentinel System and other decentralized data repositories, e.g., payer databases.

Panelists offered several ways in which the evidence ecosystem could meet payer needs. For instance, it could provide more expeditious mapping of surrogate endpoints to meaningful outcomes for AA medications. It could also be used to develop confirmatory trial evidence or serve as an external comparator arm for trials by taking advantage of existing data within managed care networks or other existing data sources. It could also offer benchmarks for morbidity, survival, and medication and resource utilization (e.g., total cost of care, emergency visits, cost avoidance, number needed to treat).

Further, improved evidence could then assist with predicting whether the anticipated treatment benefit might differ among patient subpopulations (e.g., different genetic subtypes). It could also help payers characterize the place in therapy of a particular medication or treatment sequencing if multiple regimens exist and could determine appropriate guidelines for treatment discontinuation.

Patient-centered outcomes were considered a priority by participants to incorporate into the evidence ecosystem. This included quality of life, disability, function, and caregiver burden. Participants discussed whether the FDA or Centers for Medicare and Medicaid Services (CMS) could require collection of this information, whether the tool needs to be validated for the specific condition in which it is to be used, and opportunities to leverage patient reported endpoints to collect information directly from patients. Several participants also highlighted opportunities to collaborate with patient groups and existing patient-generated registries to improve understanding and collection of information.

However, even with improved data, enhanced analytic techniques, and better partnerships, forum participants acknowledged that significant cultural and payer industry changes are needed to overcome inertia, and they shared data and learnings.

Advance Potential Policy Solutions and Practices to Reduce Financial Uncertainty

During breakout groups, participants reviewed seven policy solutions proposed to reduce the financial uncertainty associated with AA products. These included solutions intended to incentivize completion of confirmatory trials, streamline coding and reimbursement, and improve communication among interested stakeholders. Groups were tasked with listing the advantages and disadvantages of each solution, rating their potential impact on financial uncertainty, patient access, and innovation; and prioritizing them in terms of which they would recommend (Table 3).

Overall, no single policy solution was uniformly selected as a top priority because participants determined that not all would work similarly with every product scenario. Participants did note that some solutions might work best in combination with others. Findings for select policies are expanded upon below.

Policies to encourage enrollment in and completion of confirmatory trials garnered the most interest from participants, for example, the proposal that CMS leverage its existing coverage with evidence development authority to set initial optimal use criteria and provide coverage conditional to trial completion.[24] Some participants raised concerns regarding the time and CMS resources required to develop guidance and possible payment for treatments with benefits that may be unconfirmed. However, other participants appreciated that this approach would provide a standard process for developing evidence and process for retracting coverage when warranted.

Alternative pricing policies to incentivize confirmatory trials after FDA approval were also seen by participants as promising. These included increasing the federal supplemental rebate for AA products for state Medicaid programs or pricing these drugs at a marginal cost-plus approach for all payers until completion of confirmatory trials. Though it was acknowledged by forum participants, that some state programs may be disproportionately impacted by AA because they must cover nearly all-FDA approved drugs, participants generally preferred lower prices that benefitted all lines of business rather than rebates paid only to Medicaid. Pricing policies, however, were seen to potentially decrease innovation, especially for rare diseases, if initial drug revenues are limited.

Additionally, participants expressed interest in creating a voluntary payer advisory committee to advise the FDA on payer needs related to novel surrogate endpoints. Like the FDA Center for Devices and Radiological Health (CDRH) Payor Communication Task Force, a voluntary program such as this could allow the FDA, CMS, and private payers to collaborate on the development of clinical evidence for AA medications.[25] This approach would be proactive to better standardize outcomes, expand beyond the FDA-CMS parallel review, and allow for improved and early communication between stakeholders. Participants noted challenges with this proposal were the need for dedicated payer resources, the need for to ensure representation across diverse types of payer organizations and transparent deliberations, and the need for a mechanism allowing engagement potentially prior to the start of clinical trials. Additionally, they recognized that infrastructure from public and private entities, professional organizations, and funding for coordination would be needed.

One policy that primarily generated concern from participants was one in which drug developers would be required to enter into value-based agreements (VBAs) for AA medications. Most participants felt this should be a

voluntary rather than a required approach. Reasons listed included that not all medications are appropriate for these agreements, variable data collection, the administrative burden to clean and analyze data can be significant, and the limited centralization of outcomes across competing private payers. Instead, participants suggested policies to create a clearinghouse of outcomes used in contracts (absent financial details), enable state Medicaid groups to conduct pilots, and allow all stakeholders to pool learnings.

At the end of 2022, as part of the Consolidations Appropriations Act, developments have brought further attention to these policies discussed., Congress granted the FDA new authority to expedite the design and initiation of confirmatory trial plans prior to approval.[26] CMS announced a new mandatory payment method for AA medications and encouraged completion of confirmatory trials by altering provider payments.[27] Though the details of these policies are still being finalized, the findings from this partnership forum may guide the implementation of these measures. It will be important to ensure opportunities and challenges raised by stakeholders are considered to avoid unintended consequences.

Limitations

One limitation of these proceedings is that the themes identified may have differed with a different mix of participants, for example, if different organizations were represented or if those with different expertise from the same organizations contributed. Second, though case study endpoints and trial results were based on actual treatments, certain criteria were simplified to better elicit practical recommendations during the forum. Finally, the proposed policy solutions discussed were collected by AMCP from various external sources. Additional information on the expected costs, benefits, and unintended consequences of each or if they were generated de novo may have resulted in a different anticipated impact or a different set of proposals being prioritized.

Conclusion

The AA pathway offers patients with serious medical conditions expedited access to drugs with a high likelihood of clinical benefit for conditions in which an unmet clinical need exists. Participants in this forum felt that continuing to support innovation in drug development and patient access through the AA and other expedited programs was important. They also recognized payer needs to aid coverage determinations and increase stakeholder trust in the AA review process. Specifically, more robust clinical trial evidence, correlating surrogate endpoints with meaningful outcomes, and developing an evidence ecosystem to deliver information more readily were seen as key. Of the various potential policy solutions reviewed, those incentivizing the completion of confirmatory trials garnered the most discussion.

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Table 1. FDA Expedited Pathway Programs

Element	Program[1,2,3]			
	Priority Review	**Breakthrough Therapy**	**Fast Track**	**Accelerated Approval**
Pathway or designation?	Designation	Designation	Designation	Pathway
Legislative/ regulatory authority	Prescription Drug User Fee Act (PDUFA)	Section 506(a), FD&C Act	Section 506(b), FD&C Act	21CFR part 314, subpart H 21 CFR part 601, subpart E Section 506(b), FD&C Act
Year established	1992	2012	1988	1992
Drug characteristics	Offer therapeutic advance over available therapy (safety, effectiveness, diagnosis, or prevention)	Preliminary clinical evidence indicates substantial improvement over available therapy (on clinically significant endpoint[s])	• Treat serious conditions • Fill unmet medical need	• Treat serious or life-threatening conditions • Fill unmet medical need
Key feature(s)	Expedited new drug application (NDA) review (6 month vs. standard 10-month review)	• Intensive FDA guidance of efficient drug development (e.g., engagement on trial design) • Organizational commitment from the FDA • Other actions to expedite *review*	• Expedited development and review • Frequent interactions with the FDA review team • Eligible for Accelerated Approval (AA) and priority review (if criteria are met)	• Approval based on surrogate endpoint or intermediate clinical endpoint "reasonably likely to produce a clinical benefit" • Confirmatory trials required but no timeframe is specified
Impacts the FDA review or drug development?	FDA review	Both	Both	Both
Allows a rolling review of information from the company?	--	Yes	Yes	--
Is the FDA decision rescindable or is withdrawal allowed?	--	Rescindable	Rescindable	Withdrawal allowed

Table 2. Comparison of FDA Evidentiary Criteria for Surrogate Endpoints and Participant-Identified Payer Evaluation Needs

Consideration	Description	Relevant Evidence Type
FDA Evidentiary Criteria for Surrogate Endpoints[1,22]		
Causality	Is there a compelling case for surrogate being on the single direct causal pathway to disease outcome, prompting less need for evidence of universality?	• Genetics, precisely known mechanism
Biologic plausibility	Is the biology of the surrogate so compelling that it adds to the weight of empirical evidence for acceptance?	• Physiological, epidemiologic, molecular
Specificity/potential for complicating effects	Other factors affecting disease outcome, including off-target effects of drugs	• Molecular, physiological, clinical
Proportionality	To what extent does the magnitude of change in the surrogate explain the disease or the magnitude of change in disease status or burden?	• Clinical trial, observational, interventional
Universality	To what extent is there evidence across drug mechanisms or across different populations?	• Meta-analysis of clinical trial, observational, interventional
Participant Identified Payer Evaluation Needs*		
Overall evidence	• Randomized trials with active or placebo comparator vs single-arm trials • More than one clinical trial with similar treatment effect sizes and safety • Larger treatment effects with appreciable differences between treatment, comparators, and when appropriate, subpopulations • Demonstration of durability ofresponse (e.g., past 15 months), long-term safety and efficacy	• Longitudinal studies to provide longer-term safety, efficacy, and durability of response (e.g., cell and gene therapies) including understanding of treatment discontinuation • Prospective observational studies based on electronic health records and registry information

Table 2. Continued

Surrogate endpoints	• Validated when possible • Details of surrogate endpoints including their role in the patho-physiology of the condition • Understanding of measurement scales and the minimum clinically important difference • Ability to differentiate across sub-populations (e.g., genetic subtypes, disease severity, disease stage) • Correlation to meaningful clinical and/or economic outcomes • Guidance on when changes in sur-rogate endpoints are expected to inform patient discontinuation	• Systems linking surrogate endpoints (e.g., laboratory tests, clinician-rated measures) and clinical outcomes • Education and materials to aid understanding • Consistent surrogate endpoint defini-tions (e.g., provider rating scales) and improved culture for sharing informa-tion
Clinical condition	• Understanding of disease course (e.g., survival for oncology patients) • Information on subpopulations (e.g., genetic subtypes) and disease impacts • Information on comparison to existing treatments, sequencing of treatments, or when treatment dis-continuation is warranted • Patient and caregiver burden	• Longitudinal data • Patient registries with linkages to electronic health records or biomarker information • Confirmatory trials with information on sub-populations • Real-world effectiveness information, including discontinuation rates • Patient-reported or caregiver-generated outcomes • Education
Economic outcomes	• Anticipated budget impact • Impact on total cost of care due to cost offsets and ancillary treatment costs • Number needed to treat	• Patient registries with linkages to elec-tronic health records to track natural history and economic endpoints • Integrated claims information
Patient-centered outcomes	• Understanding of patient reported outcomes, quality-of-life impacts, and caregiver burden	• Standardized patient reported out-comes and quality-of-life measures • Consistency in assessment tools and reporting across health care settings and providers • Improved funding and increased use of patient-experience data

*Generated using case studies modeled on existing medications, including a disease-modifying therapy for a prevalent and progressive clinical condition, a gene-modifying therapy for a pediatric rare genetic disorder, a product to treat a common oncology condition, and a treatment for a rare oncology tumor.

Table 3: Potential Policy and Practice Solutions and Participant-Anticipated Impact on Financial Uncertainty, Patient Access, and Incentives for Innovation

Solution Description	Strengths, Disadvantages, and Considerations	Participant Anticipated Impact*		
		Financial Uncertainty	Patient Access	Innovation
Evidence Generation				
CMS leverage coverage with evidence development authority	• Strengths: • Existing authority • Ability to increase real-world evidence generation on effectiveness and safety • Centralized evidence generation enables earlier detection of safety concerns • Disadvantages: • Resource-intensive and potential political concerns could slow evidence generation • Existing authority is limited to the Medicare population with minimal impact or generalizability to other lines of business (e.g., commercial, Medicaid) • Considerations: • Private plan coverage may mimic Medicare Coverage with Evidence Development (CED) policies • May require additional legislative authority • Requires transparent evidence development and status to build trust	+	+	+
Differential federal Medicaid rebate until time of full product approval	• Strengths: • Incentive for manufacturers to complete enrollment or disclose final study results • States participating in the Medicaid Drug Rebate Program must cover most FDA-approved drugs; therefore, this reduces state financial uncertainty • Disadvantages: • Potential to increase prices for other lines of business • Diminished incentives for treatments affecting rare and orphan conditions may disproportionately affect pediatric populations • Considerations: • What level of differential rebate would be required? • At what point should most confirmatory trials be complete (e.g., three or five years)?	+	+/-	-

Table 3. Continued

Marginal cost pricing applied until time of full product approval	• Strengths • Incentive for manufacturers to complete enrollment or disclose final study results • Applicable to all payers vs a differential federal rebate only applicable to Medicaid • Ease of administration for health systems and payers • Disadvantages: • Marginal cost pricing may not result in sufficient revenues to recoup research and development costs if the patient population is small • Incentives for innovation may be limited as revenues are reduced in initial years after launch • Uncertain how pricing may be affected after completion of confirmatory trials • Considerations: • If marginal cost pricing is accepted, would coverage be mandatory?	++	++	-
Reimbursement Policy				
CMS National Coverage Decision (NCD) process for AA products	• Strengths: • Existing authority • Ability for other payers to better define patient use criteria • Centralized CMS decision improves clarity for patient access • Disadvantages: • Risk paying for treatments that are ineffective • Evidence generation for additional patient populations may be limited due to set patient use criteria • Time and staff resources to develop an NCD • Considerations: • Private plan coverage may mimic an NCD • If an NCD is in place, will a third-party identify a fair price while value is determined?	+/-	++	+

Table 3. Continued

Value-based arrangements (VBAs) for AA products	• Strengths: • Incentives for evidence generation align with payment incentives • Real-world effectiveness generated can inform value proposition and future pricing • Disadvantages: • Ability to align on outcomes for a VBA is challenging • Limited feasibility for all conditions if outcome measures are not routinely or easily collected in clinical practice • Administrative complexity for private payers with varying levels of data capacity • Considerations: • Unclear what level of risk, pricing changes would be required to make administrative burden of VBA worthwhile • Infrastructure needed to aid payer data collection • Third-party arbiter may be needed to manage contractual negotiations between manufacturer and payer • Requires consistency across organizations and lines of business to track outcomes • New regulations to permit reporting of multiple best price calculations as of July 2022 mitigate concerns related to a VBA disrupting Medicaid Best Price calculations25	++	++	+++
Coding Policy				
Allow biopharmaceutical companies to concurrently apply for HCPCS code if breakthrough designations are awarded	• Strengths: • Availability of HCPCS codes is expedited and potentially alleviates provider and billing confusion or delay • Payers are able to track uptake and use of new products vs non-specific HCPCS codes • Disadvantages: • Sufficient time for billing software or forms to be updated • Minimal impact on financial uncertainty • Considerations: • Potential for insufficient ICD-10 codes for rare conditions	+	+	+

Table 3. Continued

Communication				
Create a voluntary payer committee to advise the FDA on the consideration of novel surrogate endpoints	• Strengths: • Existing precedent in Center for Devices and Radiological Health (CDRH) Payor Communication Task Force • Ease of implementation • Subset of payers are more aware of potential surrogate measures that may be used for conditional approval, thus improving the clinical and economic planning and forecasting • Trust between regulators and payers (e.g., CMS and private payers) may increase if transparent processes are used • Disadvantages: • Committee would be advisory; recommendations could be adopted or rejected • Early engagement is required to impact clinical development programs using these endpoints • Surrogate endpoint discussion may not equate to product approval • Requires time and resources from payers, including CMS • Considerations: • Does the FDA have sufficient authority or is new legislation required? • Ensure representation across various payer types, geography, and lines of business • Need a coordinating body or application process to ensure credibility and limit bias • Are meetings public and how transparent are the recommendations?	**+/-**	**+**	**+/-**

CD=Coverage Determinations; CMS=Centers for Medicare and Medicaid Services; FDA=U.S. Food and Drug Administration; NCD=National Coverage Decision; VBA=value-based agreement

*Very Much Worse (- - -), Moderately Worse (- -), Slightly Worse (-), No Change (+/-), Slightly Better (+), Moderately Worse (++), Very Much Worse (+++)

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