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Financing and Reimbursement of Cures in the US

RESEARCH BRIEF

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Impact of FDA Guidelines on Communication between Developers and Payers on Metrics in Performance-Based Agreements.

The FDA regulates communications from pharmaceutical developers to ensure that statements about products are appropriately supported by evidence. In this Research Brief, we explore the possible impacts of these regulations on use of metrics in performance-based agreements.

CHALLENGES RELATING TO METRICS FOR PERFORMANCE-BASED AGREEMENTS (PBAS)

The use of PBAs between developers and payers has grown over the last decade (see box on next page). Payments or rebates in these agreements sometimes reflect real-world achievement of clinical trial outcomes, but it may also be beneficial to link payments to outcomes that are important for value, but were not present in clinical trials. For example, durability of outcomes beyond the clinical trial length might be an important uncertainty relating to product value. It is unclear how the FDA guidelines on communication between developers and payers may impact the use of metrics that are not part of the product label in PBAs.

Communication between developers and payers is regulated by the Food & Drug Modernization Act of 1997 (FDAMA) as modified by the 21st Century Cures Act (December 2016). While these regulations were not written with PBAs in mind, they represent the best available public information on how the FDA thinks about issues that may pertain to these agreements. The revisions by the Cures Act to section 114 of FDAMA, where the regulations regarding the promotion of health care economic information (HCEI) by developers is enumerated, were especially significant for PBAs. We walk through the implications of these changes for PBAs in four potential evidentiary scenarios below.

KEY TAKEAWAYS

The FDA does not provide direct oversight of the language in value-based agreements.

Changes to FDAMA 114 allow the use of intermediate and surrogate endpoints from a clinical trial to provide the foundation for performance metrics beyond the time horizon of the trial itself.

Post-market data is appropriate to use when setting performance metrics for PBAs.

Developers and payers would benefit from further FDA guidance concerning conversations between developers and payers about potential areas of value for a treatment.

While many different stakeholders engage in PBAs, in what follows we focus solely on the implications of FDA communications guidelines for PBAs between developers and payers.

FOUR POTENTIAL EVIDENTIARY SCENARIOS

Introduction

The Cures Act expanded the possible evidentiary foundation and uses of HCEI, but it also drew boundaries around who the FDA considers to be the appropriate audience for this information. In their post-Cures Act guidance paper, the FDA includes in this group "public and private sector payors, formulary

committees (e.g., pharmacy and therapeutics committees), drug information centers, technology assessment committees, pharmacy benefit managers, third party administrators, and other multidisciplinary entities that, on behalf of health care organizations, review scientific and/or technology assessments to make drug or device selection or acquisition, formulary management, and/or coverage and reimbursement decisions on a population basis."[1]

The FDA has indicated that it is comfortable with both loosening the guidelines for HCEI communication to payers and expanding what it considers credible scientific evidence because they understand payers to be a "sophisticated"[2] audience that is motivated and able to critically evaluate the HCEI provided to them by developers. The Cures Act also made clear that the FDA will not directly review the content of PBAs.[3]

FoCUS has identified four evidentiary scenarios that are pertinent to PBA discussions (Table 1), which are listed in order of increasing opacity relative to existing FDA communication guidelines:

- Scenario #1: Basing PBA payments on clinical trial endpoints
- Scenario #2: Basing PBA payments on endpoints used in clinical trials, but for longer-term performance
- Scenario #3: Basing PBA payments on reliable scientific evidence that came (at least in part) from outside the clinical trial
- Scenario #4: Basing PBA payments on metrics that relate to value, but for which their use in PBAs could be characterized as exploratory

Scenario #1: Clinical Trial Endpoints

In this scenario PBA payments are based only on the endpoints used in the clinical trial and for the same time horizon as was used in the clinical trial (real-world replication of clinical trial outcomes)

This situation is the most straightforward because the performance metrics are based on evidence demonstrated entirely within the scope of the clinical trial and reviewed by the FDA. It would meet the pre-Cures communication guidelines as well as the current ones.

Scenario #2: Clinical Trial Endpoints for Longer Term Performance

In this scenario, performance metrics are established between payers and developers that utilize clinical trial endpoints, but extend beyond the time horizon of the clinical trial.

Expanding performance metrics to time horizons beyond what was demonstrated in clinical trials is one of the most important benefits of PBAs for durable therapies. The Cures Act removed the stipulation that HCEI 'directly' relate to the labelled information and now simply states that "health care economic information shall not be considered to be false or misleading … if the health care economic information relates…"[4]

This change appears to reflect the need for economic modeling and value discussions to consider longer term outcomes. The FDA directly addressed this scenario in a guidance document published after the revisions to FDAMA 114. In this document, the FDA explains that "HCEI analyses

PBA Metrics	Current State	Suggested Action / FDA Clarification
1. Clinical trial endpoints	Traditionally acceptable for discussions between developers and payers	None
2. Longer-term performance on clinical trials' endpoints	The Cures Act removed the stipulation that HCEI 'directly' relate to the label in order to facilitate economic modeling, which would appear to sanction use in PBAs	FDA confirmation would be beneficial
3. Reliable scientific evidence gathered outside of clinical trials	The Cures Act enabled the sharing of off-label HCEI to sophisticated audiences when supported by competent and reliable evidence, which would appear to sanction use in PBAs	FDA confirmation would be beneficial
4. Exploratory value metrics	General discussion of potential value is essential in discussions between developer and payers and would not appear to make a claim of actual value	FDA confirmation and/or clear guidelines would be beneficial, including consideration of external communication of PBA terms and recommendations for label revisions based on actual outcomes

Table 1. Four Evidentiary Scenarios Pertinent to Performance-Based Agreement Discussions.
Note: PBAs = Performance-Based Agreements; HCEI = Health Care Economic Information

may be derived from clinical data demonstrating an effect on a surrogate endpoint that is known to predict clinical benefit (i.e., a validated surrogated endpoint) or on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit."[5]

It therefore seems clear that one of the consequences of the removal of the stipulation for HCEI to 'directly' relate to the labelled indication by the Cures Act is to allow precisely the kind of communication described in this scenario.

Scenario #3: Reliable Scientific Evidence Gathered Outside the Clinical Trial

In this scenario, evidence is used as the basis for PBA metrics that wasn't included in the FDA labelling process. This has particular importance for PBAs because it opens up the use of post-market data as a basis for performance metrics, including data gathered beyond the time horizons of clinical trials.

The Cures Act weakened the previous restrictions in FDAMA 114 pertaining to the sharing of off-label HCEI, enabling the sharing of HCEI about a product as long as it is consistent with the labelled information in terms of "the disease or condition, the manifestation of the disease or condition, or symptoms associated with the disease or condition in the patient population for which the drug is indicated in the FDA-approved labeling."[6]

Off-label HCEI must still be grounded in FDA-approved practices for the gathering of "competent and reliable scientific evidence,"[7] and any differences between label and off-label HCEI should include a disclaimer to describe "material differences between the health care economic information and the labeling approved for the drug."[8]

Former FDA Commissioner Scott Gottlieb explained that one of the data sets that this off-label HCEI can be based on is "data from post-market studies and surveillance of a product's approved uses."[9] Because the revised FDAMA 114 language now allows sharing of off-label information (within the framework described above), it is reasonable to assume that post-market studies can be the basis for performance metrics in PBAs.

Scenario #4: Metrics Not Based On FDA-Approved Evidence

In this scenario, payers and developers discuss potential areas of value that a product may provide, but for which there is not sufficient evidence in clinical trials or from post-approval studies. For example, a genetic therapy may be approved based on evidence of increased production of a target product, but payers may seek confirmation that this leads to meaningful improvements in patient health. In some cases, FDA labels may also be broader than the clinical trial population, and it may be important for payers to understand benefit in populations for which there is no evidence.

Current Clinical Outcome PBA Examples

- Zolgensma (*Novartis*) with Harvard-Pilgrim and Accredo based on clinical outcomes
- Brilinta (*AstraZeneca*) with UPMC HealthPlan based on post-heart attack cardiovascular clinical metrics
- Vivitrol (*Alkermes*) with UPMC HealthPlan based on clinical outcomes following opioid addiction
- Onpattro (*Alnylam*) with Harvard-Pilgrim based on clinical outcomes demonstrated in trial
- Repatha (*Amgen*) purchased by Cigna, Abarca, and Harvard-Pilgrim with PBAs based on LDL-cholesterol levels
- Luxturna (*Spark*) purchased by Harvard-Pilgrim with PBA based on ocular outcomes
- Multiple MS treatments (*Biogen*) purchased by Prime Therapeutics, Abarca, and Harvard-Pilgrim with PBA based on clinical outcomes
- Sovaldi and Harvoni (*Gilead*) purchased by CatamaranRx with a PBA based on clinical outcomes
- Avastin (*Genentech*) purchased by Priority Health with a PBA based on clinical outcomes of non–small-cell lung cancer

Source: Verpora US VBA Tracker, Sept 2019

Understanding of value is essential to discussions between developers and payers regarding an appropriate price for a product. Scenario 2 explicitly contemplates extrapolating from current information to gain a better understanding of likely overall value to support these discussions, and the use of additional potential outcomes seems a natural extension of this concept.

Although it seems reasonable to assume that statements about what an outcome would be worth *if* it occurs is not the same as a claim that the outcome *will* occur, this is not explicitly covered by current FDA communication guidelines. Further guidance from the FDA on this point would be beneficial for both developers and payers.

It is likely that discussions of potential value (or what would be valued) come up routinely in conversations today between developers and payers outside of the context of PBAs. These are essential elements of value conversations, and there need to be mechanisms to make these conversations allowable. However, more public conversations may need additional levels of scrutiny. Public disclosure of the use of a performance metric might create perceptions that the product could meet that metric, and outcomes from PBAs might appropriately lead to evidence important for future

discussions (Scenario 3) and perhaps even for label modification.

ABOUT FOCUS

The MIT NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US) seeks to collaboratively address the need for new, innovative financing and reimbursement models for durable and potentially curable therapies that ensure patient access and sustainability for all stakeholders. Our mission is to deliver an understanding of financial challenges created by these therapies leading to system-wide, implementable precision financing models. This multi-stakeholder effort gathers developers, providers, regulators, patient advocacy groups, payers from all segments of the US healthcare system, and academics working in healthcare policy, financing, and reimbursement in this endeavor.

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