

Chapter 1:

Addressing High-Cost Specialty Drugs

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Recommendations

1.1 Congress should amend Section 1927(c)(1) of the Social Security Act to increase the minimum rebate percentage on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased rebate percentage would apply until the manufacturer has completed the postmarketing confirmatory trial and been granted traditional FDA approval. Once the FDA grants traditional approval, the minimum rebate percentage would revert back to the amount listed under Section 1927(c)(1)(B)(i).

1.2 Congress should amend Section 1927(c)(2) of the Social Security Act to increase the additional inflationary rebate on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased inflationary rebate would go into effect if the manufacturer has not yet completed the postmarketing confirmatory trial and been granted traditional FDA approval after a specified number of years. Once the FDA grants traditional approval, the inflationary rebate would revert back to the amount typically calculated under Section 1927(c)(2).

Key Points

- State Medicaid officials have expressed concern about paying high prices for accelerated approval drugs. These are drugs approved by the FDA based on whether they have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit. This is different from traditional approval, which requires verification of the clinical benefit.
- Under the Medicaid Drug Rebate Program (MDRP), all FDA-approved drugs must be covered, including those approved under both the traditional and accelerated pathways. While manufacturers are required to conduct postmarketing confirmatory trials to verify that an accelerated approval drug achieves a clinical benefit, these trials are often delayed.
- Increasing the Medicaid rebates on accelerated approval drugs until the clinical benefit has been verified strikes a balance between addressing state concerns about paying high prices for these products while maintaining access for beneficiaries. MACPAC's recommendations make no changes to the obligation to cover these drugs.
- In this chapter, MACPAC also considers coverage and payment policies for cell and gene therapies, a subset of specialty drugs that are receiving significant attention due to their high costs and potential as durable or curable treatments.
- A new national drug benefit for cell and gene therapies could allow for new coverage, payment, or rebate requirements without disrupting the structure of the MDRP for all other outpatient drugs. This chapter looks at the issues that would need to be considered in designing such a benefit.

CHAPTER 1: Addressing High-Cost Specialty Drugs

In fiscal year (FY) 2019, Medicaid spent approximately \$66.7 billion on outpatient prescription drugs and collected \$37.1 billion in rebates, resulting in net drug spending of \$29.6 billion, or about 5 percent of benefit spending that year (MACPAC 2020a). Drug spending trends have been fairly moderate over the past few years, with annual increases between 1.4 and 4.7 percent from calendar year (CY) 2016 to CY 2019. However, the Centers for Medicare & Medicaid Services (CMS) Office of the Actuary projects Medicaid drug spending to increase between 5 and 6 percent annually over the next several years (OACT 2020).

Medicaid drug spending trends are increasingly being driven by high-cost specialty drugs.¹ From 2010 to 2015, net spending on specialty drugs in Medicaid almost doubled, growing from \$4.8 billion (25 percent of total net drug spending) to \$9.9 billion (35 percent of total net drug spending) (CBO 2019).² According to Magellan Rx Management, a leading Medicaid pharmacy benefit administrator, the net cost per claim for traditional drugs in fee-for-service (FFS) Medicaid fell by 0.4 percent from 2018 to 2019, while the net cost per claim for specialty drugs increased 8.6 percent over the same period. In 2019, specialty drugs accounted for 48.5 percent of FFS pharmacy spending but only 1.3 percent of drug utilization (Magellan 2020).

State Medicaid officials have expressed concern about the fiscal pressures created by the introduction of new specialty drugs. The launch prices for specialty drugs continue to grow, with one gene therapy for spinal muscular atrophy costing as much as \$2.1 million per course of treatment. The introduction of each new drug can add substantial costs to the Medicaid budget.

Looking forward, nearly 8,000 products are in development across all stages of the

pharmaceutical pipeline, and many of these products are specialty drugs, including nearly 400 cell and gene therapies (PhRMA 2021, 2020). While some of these therapies are expected to deliver long-term clinical benefits and could be potentially curative, the high up-front cost of specialty drugs can create significant pressure on state budgets. Additionally, many of these therapies are indicated for conditions that affect small populations—a situation that creates uncertainty about the number of individuals who might seek treatment in any given year and the potential for volatility in annual budgets of both states and health plans.

In addition, the U.S. Food and Drug Administration (FDA) is approving more products through its accelerated approval pathway, a program that allows drugs to come to market faster than under the traditional process. Under this pathway, drugs can be approved based on surrogate endpoints that are likely to predict a clinical benefit but before the clinical benefit has been demonstrated. In 2020, the FDA approved 53 novel therapies, including 12 drugs (23 percent) under the accelerated approval pathway (FDA 2021a).

States have expressed concern about paying high list prices when these products do not have a verified clinical benefit. The FDA requires that manufacturers conduct confirmatory trials to verify the clinical benefit of drugs receiving accelerated approval, but many of these trials are delayed and can take more than 10 years to complete (Chen 2018, Naci et al. 2017).

MACPAC has consistently heard from states that the utilization management tools permitted under Medicaid law are ineffective in containing costs for high-cost specialty drugs (Brown 2017). Although states have started to develop some innovative strategies to deal with particular high-cost specialty drugs, such as a subscription model to pay for hepatitis C drugs, they are seeking new tools, some of which may require new authorities, to address high-cost specialty drugs more broadly (Gee 2018, Jeffrey 2018). In a recent survey, over two-thirds of states responded that developing policies and

strategies related to new high-cost therapies was a top priority (Gifford et al. 2020).

As a result, MACPAC has been focusing on how to address concerns about the high and growing costs associated with specialty drugs, while also ensuring that beneficiaries who could benefit from these new therapies still have access to them. To assist in the Commission's efforts, MACPAC worked with a contractor to conduct an analysis of the drug pipeline and convene a technical advisory panel (TAP) of drug policy and pricing experts from academia and the private sector, state Medicaid and federal officials, beneficiary advocates, providers, health plans, and drug manufacturers. The goal was to bring together a diverse group of experts to help the Commission prioritize which drugs in the pipeline could have a significant effect on Medicaid over the next three to five years, identify what challenges these drugs present, and suggest new Medicaid payment and coverage policies that could help address these challenges. As a part of this work, we identified a discrete, but important, first step to address state concerns: increasing the rebate on accelerated approval drugs until the clinical benefit has been confirmed.

This chapter presents the Commission's recommendations on increasing the statutory Medicaid rebates on drugs receiving accelerated approval until the clinical benefit has been verified. Specifically:

- Congress should amend Section 1927(c)(1) of the Social Security Act to increase the minimum rebate percentage on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased rebate percentage would apply until the manufacturer has completed the postmarketing confirmatory trial and been granted traditional FDA approval. Once the FDA grants traditional approval, the minimum rebate percentage would revert back to the amount listed under Section 1927(c)(1)(B)(i).
- Congress should amend Section 1927(c)(2) of the Social Security Act to increase the additional inflationary rebate on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased inflationary rebate would go into effect if the manufacturer has not yet completed the postmarketing confirmatory trial and been granted traditional FDA approval after a specified number of years. Once the FDA grants traditional approval, the inflationary rebate would revert back to the amount typically calculated under Section 1927(c)(2).

These changes would address states' concerns by reducing the net cost for the subset of drugs approved through the accelerated approval pathway, while preserving beneficiary access to these drugs under the terms of the Medicaid Drug Rebate Program (MDRP). The Commission is not recommending a specific increase in the rebates but notes that the amount needs to be significant enough to provide a meaningful reduction in spending and provide a strong incentive to encourage completion of the confirmatory trial, but not so large as to discourage development of drugs for conditions that disproportionately affect Medicaid beneficiaries. These recommendations do not alter the FDA accelerated approval pathway or change the obligation of states to cover accelerated approval drugs.

This chapter begins with an overview of the MDRP. It continues by detailing the findings from MACPAC's TAP. It then discusses the accelerated approval pathway and the concerns that the use of surrogate endpoints in the approval process creates for payers. The chapter then presents the rationale for the Commission's recommendations for Congress to increase the rebates on accelerated approval drugs until the clinical benefit has been verified.

The TAP also discussed issues related to cell and gene therapies and provided the Commission with a framework for developing a new benefit for

coverage and payment of these therapies. The Commission discussed these ideas in its public meetings and decided that while it was premature to make recommendations, it would be useful to share an analysis of the key design options and the potential trade-offs that would need to be considered when developing such a benefit in this report. Our analysis also considers implications for certain stakeholders. The chapter concludes by discussing considerations for a national drug registry and outlining the Commission's future work in this area.

Medicaid Drug Rebate Program

The Medicaid Drug Rebate Program was created under the Omnibus Budget Reconciliation Act of 1990 (P.L. 101-508) with the purpose of ensuring that Medicaid pays a net price that is consistent with the lowest or best price that manufacturers charge other payers for the drug. Under the program, a drug manufacturer must enter into a Medicaid national drug rebate agreement with the Secretary of the U.S. Department of Health and Human Services (the Secretary) in order for states to receive federal funding for using the manufacturer's products (§ 1927(a)(1) of the Social Security Act (the Act)).³ In exchange for the rebates, state Medicaid programs generally must cover all of a participating manufacturer's drugs when prescribed for a medically accepted indication, although the states may limit the use of some drugs through preferred drug lists (PDLs), prior authorization, and quantity limits.⁴

Coverage and access

Under the MDRP, a drug meets the definition of a covered outpatient drug if its manufacturer has in place a rebate agreement with the Secretary and the drug has been approved by the FDA (§ 1927(k) of the Act). This means that a state is generally required to cover all of a participating

manufacturer's products as soon as they have been approved by the FDA and enter the market—that is, when they are available for sale by the manufacturer in the state.⁵ Although a state can use prior authorization, clinical criteria, or other utilization management tools to manage the use of a particular drug, the effect of these limitations “should not result in the denial of access to effective, clinically appropriate, and medically necessary treatments” (CMS 2015, p. 3).

Medicaid's requirement to cover essentially all FDA-approved drugs makes the program unique among payers. In general, plans sold on health insurance exchanges and Medicare Part D plans have minimum requirements for drug coverage, but they are allowed to exclude coverage for some drugs.⁶ Likewise, self-insured plans, large group plans, and grandfathered health plans not subject to essential health benefit requirements can exclude coverage for some drugs. This Medicaid coverage requirement limits states' ability to manage utilization and spending and to negotiate rebates with manufacturers compared with other payers.

Statutory rebates

Medicaid drug rebates are calculated based on average manufacturer price (AMP). AMP is defined as the average price paid to the manufacturer for the drug in the United States by wholesalers for drugs distributed to retail community pharmacies and by retail community pharmacies that purchase drugs directly from the manufacturer (§ 1927(k)(1) of the Act).⁷

The rebate formula for single source and innovator multiple source drugs (i.e., brand-name drugs) differs from the formula for non-innovator multiple source drugs (i.e., generic drugs).⁸ For purposes of simplicity, this chapter refers to single source and innovator multiple source drugs as brand drugs and refers to non-innovator multiple source drugs as generic drugs or generics.

The rebate amount for covered outpatient drugs has two components: a basic rebate amount and

an additional inflationary component. For most brand drugs, the basic rebate amount is equal to either 23.1 percent of AMP or AMP minus best price, whichever is greater.⁹ Best price is statutorily defined as the lowest price available to any wholesaler, retailer, provider, or paying entity, excluding certain governmental payers (§ 1927(c)(1)(C) of the Act).¹⁰ For generic drugs, the basic rebate amount is calculated as 13 percent of AMP with no best price provision.

An additional rebate based on an inflationary component is added if the increase in a drug's AMP exceeds the increase in the Consumer Price Index for All Urban Consumers (CPI-U) over time. The inflationary component is equal to the amount that the drug's current quarter AMP exceeds its baseline AMP trended to the current period by the CPI-U.¹¹ This inflationary rebate is designed to limit the increase in the net price of any drug to the rate of inflation.

Until January 1, 2024, the total rebate amount (the sum of the basic and inflationary components) cannot exceed 100 percent of AMP (§ 1927(c)(2)(D) of the Act). The American Rescue Plan Act of 2021 (ARP, P.L. 117-2) removes this cap on Medicaid rebates beginning January 1, 2024 (§ 9816 of ARP).

Supplemental rebates

A state can negotiate with manufacturers to obtain supplemental rebates, which manufacturers provide to ensure that their products are placed on the state's PDL. As of December 2020, almost all states (46 states and the District of Columbia) were receiving supplemental rebates in addition to mandated federal rebates (CMS 2020).¹² Preferred drugs typically face fewer utilization management requirements (e.g., prior authorization) than therapeutically equivalent drugs that are not on the list, and this results in a shift in market share to the preferred drugs. Some states pursue supplemental rebate agreements on their own, while others have joined multistate coalitions for negotiation purposes (CMS 2020).

Developing New Models

To assist in the Commission's examination of the effects of high-cost specialty drugs on Medicaid, as noted above, MACPAC worked with a contractor to conduct an analysis of the drug pipeline and convene a TAP to examine these issues more closely. The TAP included drug policy and pricing experts from academia and the private sector, state Medicaid and federal officials, beneficiary advocates, providers, health plans, and drug manufacturers. Over the course of three meetings, the panel prioritized which drugs in the pipeline could have a significant effect on Medicaid, what challenges these drugs present, and what changes to Medicaid payment and coverage policies could help address these challenges.

Drug pipeline

MACPAC's contractor analyzed all specialty drugs currently in Phase I-III trials or drugs under FDA review.¹³ Given the number of drugs in the pipeline, the analysis prioritized later-stage products that are likely to have the greatest effect on Medicaid in the next three to five years based on expected cost and patient population (NORC 2020).

The pipeline analysis highlighted three types of high-cost specialty drugs that will have a significant or disproportionate effect on Medicaid:

- High-cost pediatric drugs. Because more than two out of every five children are Medicaid beneficiaries, high-cost pediatric products are of particular importance for Medicaid (MACPAC 2020b). Several high-cost cell and gene therapies with pediatric indications in the pipeline could generate high total spending even with relatively few eligible patients. Currently, 186 drugs with pediatric indications are in development across all clinical trial phases. Among them are 45 cell or gene therapies, which are indicated to treat children with sickle cell disease, leukemia/lymphoma, muscular dystrophy, and achromatopsia. In addition to gene

therapies, several specialty drugs for cystic fibrosis are in the pipeline. A large proportion of children with these conditions are expected to be covered by Medicaid because these conditions are often qualifying disabilities for Medicaid eligibility.

- **Adult gene and cell therapies.** Even though Medicaid is not likely to be the largest payer for gene and cell therapies indicated for adults, any utilization of these high-cost products may strain Medicaid budgets. Focusing specifically on therapies nearing FDA approval, 61 gene and cell therapies indicated for adults are in Phase III or later (e.g., a new drug application has been submitted). Among these therapies, 24 are indicated for various types of cancers. Products for hemophilia, autoimmune diseases, diabetes, and cardiovascular disease could also have significant Medicaid utilization. For example, four hemophilia gene therapies in Phase III trials are expected to launch in the next few years. Another hemophilia A product is currently under FDA review but will require two more years of clinical trial data prior to approval. It is expected to have a launch price between \$2 million and \$3 million.
- **Other specialty drugs.** Beyond cell and gene therapies, Medicaid drug spending will be driven by specialty products with moderately high prices, significant utilization, and higher incremental costs relative to the current treatments. Currently, 282 specialty drugs are in Phase III clinical trials or under FDA review. The three therapeutic areas with the largest number of drugs in development are oncology (78 products), autoimmune diseases (33 products), and COVID-19 treatments (19 products). Other therapeutic areas with a number of drugs in development are those that treat genetic disorders, hematologic conditions, and infectious diseases.

Challenges for state Medicaid programs

After reviewing the findings from the pipeline analysis, the TAP participants broadly agreed that three types of drugs should be prioritized for further discussion and model development given their potential effect on Medicaid. They include: (1) cell and gene therapies for adults and children, (2) drugs approved through the accelerated approval pathway, and (3) specialty high-cost drugs for highly sensitive populations. Each of these drug types have attributes that make them challenging to manage under the MDRP, described briefly below:

- **High up-front costs.** Products with extremely high list prices and a short duration of use create sudden spikes in Medicaid spending, rather than consistent monthly costs. Gene and cell therapies can have list prices of more than \$1 million per course of treatment. Though such products have the potential to reduce other medical spending over a beneficiary's lifetime, these high up-front costs are difficult to manage for states, which operate within annual budgets.
- **Budget volatility.** Many extremely high-cost specialty drugs are indicated for conditions that affect a small population, which creates uncertainty about the number of individuals who will seek treatment in any given year. As a result, their effects on state spending can be extremely variable from year to year and make it difficult to predict and manage annual pharmacy costs. Unexpected increases in drug spending can also be challenging for Medicaid managed care plans that have annual capitated contracts, which cannot easily accommodate sudden increases in spending (e.g., the rapid, new spending that occurred when new hepatitis C medications launched at the end of 2013).
- **Uncertain long-term benefit.** While some of these drugs may lead to reductions in other medical spending for beneficiaries, these

reductions may take many years to materialize. Moreover, some therapies for conditions with few treatment options may have significant clinical benefits but never realize savings that offset the drug purchase price. Additionally, Medicaid-funded treatments may yield future cost savings for other payers, such as commercial insurers or Medicare.

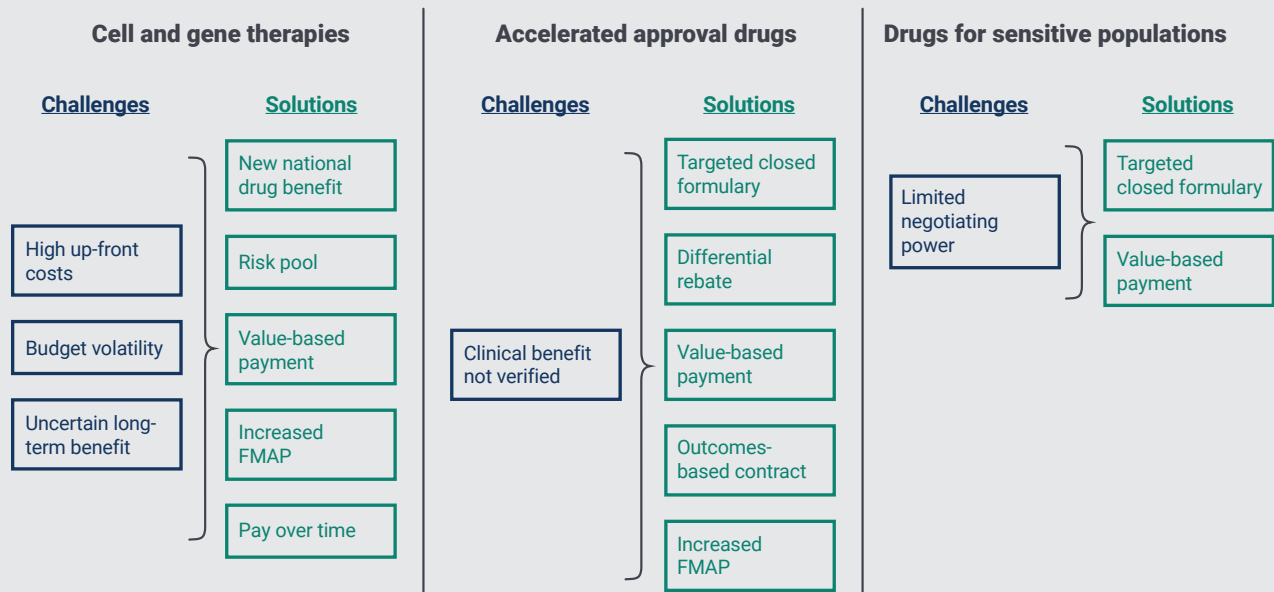
- **Clinical benefit not verified.** Traditional FDA approval requires that a clinical benefit be shown before approval can be granted. The accelerated approval pathway allows for drugs to be approved based on surrogate or intermediate clinical endpoints that are likely to predict a clinical benefit, even though the clinical benefit has yet to be verified. Payers have expressed concern that the launch prices of these drugs do not reflect that the clinical benefit has not yet been verified. Moreover, while the FDA requires

drug manufacturers to conduct postmarketing trials to verify the clinical benefit, these trials are often delayed and payers may be covering drugs for several years that ultimately do not confer a clinical benefit.

- **Limited negotiating power.** State Medicaid programs have limited ability to negotiate rebates for drugs that have no or limited therapeutic competition, or for conditions for which most or all of the drugs in a particular class (e.g., HIV/AIDS treatments) fall under broad federal or state mandates to cover these drugs with little to no restrictions (e.g., no preferred drug list).

TAP participants identified the specific challenges to Medicaid associated with each of the three priority drug types and mapped potential models to address those challenges (Figure 1-1).

FIGURE 1-1. Drug Types, Challenges, and Solutions



Note: FMAP is federal medical assistance percentage.

Source: NORC and MACPAC, 2021, findings from Technical Advisory Panel.

Models considered by the TAP included:

- new national drug benefit: coverage outside of the MDRP in which the federal government would purchase certain high-cost products, such as cell and gene therapies;
- risk pool: multistate or national purchasing pool for high-cost drugs that treat small patient populations;
- value-based payment: payment based on a third-party assessment of the drug's value;
- increased federal medical assistance percentage (FMAP): higher federal match for a specific set of high-cost therapies;
- pay over time: amortize payments for high-cost, short-duration therapies over a longer period of time;
- outcomes-based contract: higher rebates if the drug does not achieve a specified clinical outcome;
- differential mandatory rebates: higher mandatory rebates for certain products; and
- targeted closed formularies: allow states to deny coverage for certain drugs.

These models are not mutually exclusive and could be combined.

For accelerated approval drugs, the TAP participants briefly discussed allowing states to implement a commercial-style closed formulary that would allow them to exclude coverage of accelerated approval drugs while the clinical benefit has yet to be verified. Many participants had concerns that a closed formulary would limit access to beneficiaries and that other options could address the issue without removing Medicaid's coverage requirement.

They also discussed setting a price based on an independent assessment of value or developing mandatory outcomes-based contracts for Medicaid. The participants agreed that it would be difficult to assess value or to identify appropriate outcome

targets until the specific level of clinical benefit was known and verified. These models could be useful once the clinical benefit has been verified, but they would not address the challenges that payers face while the manufacturer is conducting the confirmatory trial. Moreover, states already face substantial challenges in implementing value- or outcomes-based models (Gifford et al. 2020).¹⁴

Participants also discussed increasing the FMAP but decided against this option; while an increased federal match would decrease state spending, it would shift costs to the federal government and not decrease overall Medicaid spending.

Given these concerns, the TAP participants identified a differential rebate on accelerated approval drugs as the best option because it strikes a balance between reducing Medicaid costs while still maintaining access.

With respect to cell and gene therapies, the TAP explored a wide variety of payment and rebate models that could be used to address the challenges of the high up-front costs, budget volatility, and uncertainty about long-term benefits. Because of the small size of the target population for many of these products, panel participants discussed the need to aggregate the populations to create a more predictable pool of patients, to smooth risk by reducing annual state or plan-to-plan variation in spending, and to increase leverage in negotiations with manufacturers. This could be accomplished through a new national benefit or a national risk pool.

On pricing, participants agreed that volume-based rebates would not be sufficient to reduce costs and that other mechanisms would be necessary to reduce the price of these therapies. They discussed setting prices based on an independent assessment of value, allowing states to pay for the drugs over time, or using outcomes-based contracts. Additionally, due to the extremely high cost of these products and the potential for long-term benefits to accrue to other payers, many participants thought that the federal government could increase the FMAP or cover the cost of these therapies completely.

Ultimately, the TAP noted, and the Commission agreed, that creating a new benefit for cell and gene therapies had the most potential because it would aggregate the population into a more predictable risk pool and allow for new coverage, payment, or rebate requirements without disrupting the existing structure of the MDRP for all other outpatient drugs. Some combination of the other models could be implemented under the new benefit without creating unintended consequences for coverage of or rebates on other drugs.

The third area the TAP identified as a priority was drugs used to treat sensitive populations. This category includes drugs that treat debilitating conditions for which few to no treatment options exist (e.g., spinal muscular atrophy), as well as more manageable conditions, such as HIV/AIDS. Historically, states have had limited ability to manage these drug classes and as a result have limited negotiating power with manufacturers. Participants discussed the idea of a targeted closed formulary in which states would have narrow exclusionary capabilities based on sound clinical criteria. Formularies could be developed to ensure access to a minimum number of products. Additionally, narrow exclusions of certain products, such as line extensions and combination products, would allow states to provide broad access to all the chemical entities but give them additional leverage in supplemental rebate negotiations with manufacturers. Participants also discussed the idea of developing a value-based payment policy using an independent assessment. However, the panel had difficulty narrowing down the options and ultimately did not settle on any particular model. Many TAP participants noted that states may not be able to fully use any new tools or models due to existing state laws. For example, some states have laws requiring coverage of all HIV/AIDS drugs with minimal or no restrictions.

The findings from the TAP were helpful in informing the Commission's work. After deliberating on the various policy options and key design considerations that came from the TAP, the Commission decided to make recommendations

for a differential rebate on accelerated approval drugs. In the Commission's view, the creation of a new drug benefit for cell and gene therapies has potential. However, we are not ready to make a recommendation on this model at this time. We discuss both of these models in greater detail below.

Accelerated Approval

The FDA has programs that expedite development and review of new drugs that address an unmet medical need for a serious or life-threatening condition. The accelerated approval pathway allows the FDA to grant approval more quickly than the traditional approach because it allows approval based on whether the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit (§ 506(c) of the Federal Food, Drug, and Cosmetic Act).¹⁵ A surrogate endpoint is a marker—a laboratory measurement, radiographic image, physical sign, or other measure—that is thought to predict clinical benefit, but is not itself a measure of clinical benefit (FDA 2014). Surrogate endpoints are essentially a proxy for a clinical benefit. For example, tumor shrinkage in certain cancer types has been considered reasonably likely to predict improvement in overall survival and is a commonly used surrogate endpoint in the accelerated approval of cancer drugs (Chen 2018, FDA 2014).

When the FDA approves a drug through the accelerated approval pathway, it requires manufacturers to conduct additional postmarketing studies (sometimes called Phase IV studies) to verify that the drug achieves a clinical benefit (21 CFR 314.510, 21 CFR 601.41, FDA 2014).¹⁶

Risk of surrogate endpoints

The FDA has acknowledged that using surrogate endpoints creates a risk that patients could be exposed to a drug that later was shown not to provide an actual clinical benefit. It has also noted that because accelerated approval may rely on

smaller or shorter clinical trials than used under traditional approval, this pathway may result in less information about the occurrence of rare or delayed adverse events (FDA 2014). A common criticism is whether surrogate endpoints are actually predictive of a clinical benefit and thus, better health outcomes. For example, studies have called into question whether tumor shrinkage, a common surrogate endpoint, is sufficiently correlated with better survival rates (Chen 2018, Pietrangelo 2017). Critics point to these risks when raising concerns that the accelerated approval pathway results in less effective and potentially dangerous drugs entering the market (Chen 2018, CMS 2017, Kesselheim and Avorn 2016).

Critics also point out that some drugs granted accelerated approval have been rejected by the FDA's European counterpart, the European Medicines Agency (EMA). For example, the FDA approved both Folutyn, used to treat peripheral T-cell lymphoma, and Exondys 51, used to treat Duchenne muscular dystrophy, through the accelerated approval pathway, while the EMA denied these applications (Chen 2018; EMA 2018, 2012; Pollack 2016). Disagreement on the approval of a particular drug can occur even within the FDA. Some FDA staff members thought that the evidence presented for Exondys 51 did not demonstrate that the drug was reasonably likely to produce a clinical benefit. They appealed the approval decision, but the approval was upheld (Box 1-1).

Delay in postmarketing confirmatory trials

As noted above, the FDA requires manufacturers to conduct postmarketing studies to verify and describe the clinical benefit. These trials must be completed with due diligence (21 CFR 314.510 and 601.41). The FDA has interpreted due diligence to mean that such trials must be conducted promptly to facilitate the determination of whether a clinical benefit has been verified as soon as possible (FDA 2014). However, there are not clear standards on how long these postmarketing studies should take,

and they are often delayed. One analysis found that results from confirmatory trials for over half of indications granted accelerated approval between 2009 and 2013 were not available after a median of five years of follow-up (Naci et al. 2017). Some confirmatory trials can take 10 years or longer (Chen 2018). By comparison, the FDA states it normally takes an average of one to four years for Phase III clinical trials under the traditional pathway (FDA 2018).

Some practical reasons exist for delays in the postmarketing trials. For example, finding and recruiting patients willing to participate in drug trials among the small populations affected by rare diseases can be challenging. However, there is also a concern that drug manufacturers do not have the same financial incentives to complete these trials as they do with Phase III clinical trials under the traditional pathway. This concern exists because accelerated approval products generate revenue, and a negative finding from a confirmatory trial could reduce those revenues and even result in the drug being pulled from the market (Chen 2018).

BOX 1-1. Controversial Approval of Exondys 51

In 2016, the FDA granted accelerated approval to Exondys 51 (eteplirsen), a treatment for Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation in the dystrophin gene that can be treated by skipping exon 51 (FDA 2016a). Exondys 51 costs about \$300,000 per year but can run up to \$1 million annually based on a patient's weight (Thomas 2017).

The drug's approval was controversial. The FDA's advisory committee of external experts voted against granting accelerated approval. The advisory committee members who voted no commented that the applicant did not provide substantial evidence that the drug is reasonably likely to produce a clinical benefit (FDA 2016b). The director of the Center for Drug Evaluation and Research overrode the committee's recommendation and granted accelerated approval to Exondys 51. Some FDA staff expressed concern and appealed the approval decision to the FDA commissioner, who ultimately upheld the approval decision (FDA 2016c). Because of the controversy surrounding Exondys 51's approval, many commercial payers declined to cover the drug or only covered it in limited circumstances (Thomas 2017).

In 2018, Sarepta Therapeutics, the manufacturer of Exondys 51, sought accelerated approval for Vyondys 53 (golodirsen), a similar drug that would treat DMD in patients who have a confirmed mutation in the dystrophin gene that can be treated by skipping exon 53. The initial approval was denied, and as a part of the complete response letter, the FDA pointed out that the manufacturer had yet to initiate the required confirmatory trial for Exondys 51 two years and 11 months after its approval. The complete response letter noted that if the manufacturer had begun the trial, additional evidence could have been available to assess the likelihood that small amounts of truncated dystrophin would lead to a clinical benefit (FDA 2019a). The manufacturer appealed the decision, and Vyondys 53 was granted accelerated approval in December 2019 (FDA 2019b). Subsequently, in February 2021, the FDA granted Sarepta accelerated approval for Amondys 45 to treat patients amenable to exon 45 skipping (FDA 2021b). Three drugs have been approved based on the same surrogate endpoint that created significant disagreement within the FDA and without any additional evidence to demonstrate the relationship between the surrogate endpoint and the clinical benefit.

As part of the original approval letter for Exondys 51, Sarepta agreed to a timeline in which the postmarketing confirmatory trial would be completed in 2020 with a final report submission in 2021 (FDA 2016a). Information from the U.S. National Library of Medicine's clinical trial database indicates that the confirmatory trial for Exondys 51 started in July 2020 and is estimated to be complete in February 2026, a delay of five to six years from the initial timeline agreed upon in the original approval letter (ClinicalTrials.gov, NCT03992430, FDA 2016a).

State concerns

The MDRP requires states to generally cover all of a participating manufacturer's products as soon as they have been approved by the FDA and enter the market. This coverage requirement includes drugs approved under the accelerated approval pathway (CMS 2018a). State Medicaid officials have expressed concern about the requirement that Medicaid cover these drugs when additional studies are still needed to verify their clinical benefit (CMS 2019, 2017). In particular, they have shared concerns about paying high list prices when these products do not have a verified clinical benefit, and in some cases, may cause harm to vulnerable patients. They are wary about paying for therapies that ultimately do not demonstrate a clinical benefit, as was the case with Makena. This drug, used to reduce the risk of preterm birth, received accelerated approval in 2011. In October 2020, the FDA proposed that the drug be pulled from the market because the postmarketing study failed to show clinical benefit (FDA 2020a).¹⁷

In addition, the length of time taken to complete some confirmatory trials means that states may be paying for high-cost treatments for several years before the benefit is verified. The case of Exondys 51 makes this clear. In the initial terms of its approval in 2016, the confirmatory trial for Exondys 51 was to be completed by 2020 (FDA 2016a). The manufacturer recently indicated the trial began in 2020 and is not estimated to be complete until 2026, meaning that state Medicaid programs will be required to cover this drug for 10 years without confirmation of its clinical effectiveness (ClinicalTrials.gov, NCT03992430).

State Medicaid officials are particularly concerned about these issues given that the number of drugs approved through the accelerated approval pathway has been increasing. Over the five-year period of 2015 to 2019, 31 drugs (14.1 percent of all approved drugs during that period) were approved through the accelerated approval pathway. By comparison, the same number of drugs received accelerated approval in the 10-year period of 2005 to 2014, and

they represented 11.5 percent of all drugs approved in that time frame (FDA 2020b).

Commission Recommendations

In this report, the Commission recommends two changes to the Medicaid Drug Rebate Program. It is important to note that should Congress make these changes, Recommendation 1.1 is the primary recommendation and does not require the adoption of Recommendation 1.2. Recommendation 1.2 should only be adopted in conjunction with Recommendation 1.1. The rationale and implications of these recommendations are described below.

Recommendation 1.1

Congress should amend Section 1927(c)(1) of the Social Security Act to increase the minimum rebate percentage on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased rebate percentage would apply until the manufacturer has completed the postmarketing confirmatory trial and been granted traditional FDA approval. Once the FDA grants traditional approval, the minimum rebate percentage would revert back to the amount listed under Section 1927(c)(1)(B)(i).

Recommendation 1.2

Congress should amend Section 1927(c)(2) of the Social Security Act to increase the additional inflationary rebate on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased inflationary rebate would go into effect if the manufacturer has not yet completed the postmarketing confirmatory trial and been granted traditional FDA approval after a specified number of years. Once the FDA grants

traditional approval, the inflationary rebate would revert back to the amount typically calculated under Section 1927(c)(2).

Rationale

We recommend that Congress increase the statutory rebates on drugs receiving accelerated approval to lower the net price of these products until the manufacturer completes its postmarketing confirmatory trial and verifies the clinical benefit of the drug. This increased rebate would apply to all products approved through the accelerated approval pathway that have not yet completed confirmatory trials.¹⁸ Given that the FDA has an existing process to convert an accelerated approval to a traditional approval, once confirmatory trials are completed and the FDA grants traditional approval, the higher rebates would be removed and existing rebates under the MDRP (e.g., 23.1 percent of AMP) would apply (FDA 2020c).¹⁹

Changing the rebates under the MDRP strikes a balance between addressing state concerns of paying high prices for products that do not have a verified clinical benefit while maintaining Medicaid coverage for these products. Because accelerated approval drugs meet the definition of covered outpatient drugs under the MDRP, states would still be required to cover these products. The increased rebates would allow states to pay less until the manufacturer verifies the clinical benefit of the drug.

Increasing the minimum rebate would lower the net price and would help account for the risk that the product might not achieve the anticipated clinical benefit. The higher minimum rebate would also create a financial incentive for manufacturers to complete confirmatory trials in a timely manner.

An increase in the inflationary rebate would help mitigate any large increases in list price that could occur before the manufacturer completed the confirmatory trial. This increase would not go into effect for a specified number of years (e.g., five years) to provide manufacturers with a reasonable amount of time to complete the confirmatory trial but would penalize lengthy delays. In short, it would

provide an additional incentive for manufacturers to demonstrate the effectiveness of their products in a timely manner. Because this increase would be tied to the inflationary rebate, it would not be applied if the manufacturer did not increase the price faster than inflation.

Once the FDA grants traditional approval, the rebate amounts would revert back to the standard amounts calculated under the MDRP. This would effectively serve to increase the net price for the manufacturer once it had verified the drug's clinical benefit.

The Commission is not recommending a specific increase in the minimum or inflationary rebate, nor the specific number of years after which the increased inflationary rebate would apply. We consider these decisions to be matters for Congress as we do not have empirical data to make these determinations. But the Commission notes that the rebate amount needs to be significant enough to provide a meaningful reduction in Medicaid spending and to provide a strong incentive for drug manufacturers to complete confirmatory trials. When asked about the rebate amount, most TAP participants suggested that the increase in the minimum rebate for accelerated approval drugs should be higher than the 8 percentage point increase in the minimum rebate provided under the Patient Protection and Affordable Care Act (ACA, P.L. 111-148, as amended). However, too high a rebate could discourage manufacturers from investing in the development of drugs for conditions that disproportionately affect Medicaid beneficiaries.

Manufacturers have commented that they oppose this policy and argue that additional Medicaid rebates may discourage research and development or delay the market availability of drugs for serious conditions that may disproportionately affect Medicaid beneficiaries. They argue that accelerated approval drugs are not approved under lower evidentiary standards and point to FDA guidance that states “drugs granted accelerated approval must meet the same statutory standards for safety and efficacy as those granted traditional approval”

(FDA 2014). However, as noted previously, the FDA has also acknowledged that using surrogate endpoints under the accelerated approval pathway creates a risk that patients could be exposed to a drug that ultimately is shown not to provide an actual clinical benefit (FDA 2014). The recommendations do not dispute the FDA's decision to approve the drug; rather, the Commission is focused on how Medicaid pricing can be used to lower the net price to account for the fact that clinical benefit is not verified.

In terms of the effect of increased rebates on manufacturer behavior, it is important to note that manufacturers take several factors into account, including Medicaid rebates, when making decisions on drug development and product launch. First, Medicaid is not the sole payer for these drugs, so an increased rebate would not necessarily have a significant influence on a manufacturer's decision to pursue this pathway or drug development. For example, in 2010, the ACA increased the minimum rebate on brand drugs from 15.1 percent of AMP to 23.1 percent of AMP. While we do not know whether this caused any manufacturer to forgo a drug candidate, no decline occurred in drug development in the aggregate. A record number of drugs have been approved since the ACA increase in the Medicaid rebate. For example, an average of 25.5 new drugs were approved per year between 2000 and 2009, compared with an average of 37.8 new drugs approved per year between 2010 and 2019 (FDA 2020b).

Second, manufacturers would still benefit from the accelerated approval pathway as it would provide earlier access to the market and allow their drugs to generate revenue and establish market share while their confirmatory trials are underway. Manufacturers would need to weigh the cost of the additional rebates with the benefit of early market access, which could allow manufacturers to establish their products before competitors enter the market. Finally, an increased rebate would create a financial incentive for manufacturers to complete the confirmatory trial in a timely manner. The reset of the rebate back to the standard

amount once the drug converts to traditional FDA approval would equate to an increase in the net price to Medicaid and, therefore, in revenue to the manufacturer.

It is possible that increasing rebates would create an incentive to launch drugs at higher prices or attempt to shift costs to other payers. However, the extent to which manufacturers may be able to raise prices is unclear. Some economists believe that manufacturers already have the incentive to launch drugs at the maximum price the market will bear, regardless of the level of Medicaid rebates (Kaltenboeck and Bach 2018, Kesselheim et al. 2016). Even if manufacturers can raise prices to offset much of the cost of the increased rebates, they would still have an incentive to complete the confirmatory trial in a timely manner because conversion to traditional approval would lead to additional revenue.

Beneficiary advocates have also expressed concerns that access to innovative therapies could be decreased if manufacturers reduce research and development in, or delay the availability of, new therapies that treat serious conditions. In particular, advocates have expressed concern that manufacturers could reduce investment in rare conditions as manufacturers may be more sensitive to price changes for drugs that treat small populations or indications.

However, increasing the rebate on accelerated approval drugs could potentially increase beneficiary access to these products once they enter the market, particularly relative to other proposed policies. Due to their concerns about paying high prices when accelerated approval drugs do not have a verified clinical benefit, states are seeking to limit coverage of these products, which could reduce beneficiary access. Beneficiary advocates have expressed concerns that access to many of these accelerated approval drugs has been limited because some states have implemented restrictive coverage and prior authorization criteria.

Additionally, Massachusetts and Tennessee have requested Section 1115 demonstration waivers that would allow the state to implement a closed formulary, meaning that the state would not have to cover all FDA-approved drugs under the MDRP and could choose to exclude certain drugs or classes of drugs. These states specifically requested authority to exclude coverage of accelerated approval drugs because state officials believe the high prices of these drugs do not lead to prudent fiscal administration when the clinical benefit has yet to be verified (CMS 2019, 2017).²⁰ Earlier this year, CMS approved Tennessee's request to implement a closed formulary while still receiving the MDRP rebates—the first time this has been allowed (CMS 2021). Although Tennessee's demonstration approval was authorized as part of its modified block grant financing structure, this approval could provide a legal framework for other states to seek a closed formulary to exclude coverage of accelerated approval drugs.

Implications

Federal spending. The increased rebate would reduce net spending for accelerated approval products. Because the recommendations do not include specific amounts for the rebate increase, the Congressional Budget Office (CBO) provided estimates assuming a 10 percentage point increase for the minimum rebate and a 20 percent increase in the inflationary rebate if the confirmatory trial had not been completed after five years. Assuming these rebate changes would be implemented in FY 2022, the CBO estimates that these recommendations would decrease federal spending by \$0 to \$50 million in the first year and \$0 to \$1 billion in the first five years, compared with the current law baseline. To provide context for these savings, the CBO estimated that gross Medicaid spending (i.e., before rebates) on accelerated approval drugs in FY 2019 was approximately \$1 billion, including both federal and state spending.

States. State spending would decrease because states would receive the non-federal share of the increase in rebate amounts. This change

theoretically could affect supplemental rebates; however, it is unlikely that states would receive significant supplemental rebates on these products because they are unlikely to have much competition. States would still be required to offer coverage for these products.

Enrollees. Because this rebate would be implemented under the MDRP, coverage of accelerated approval drugs would not change. Beneficiaries would still have access to accelerated approval drugs once they entered the market. If manufacturers decided to forgo the accelerated approval pathway, beneficiaries might have to wait longer for those drugs to come to market. However, beneficiary access to these products could improve if states were willing to reduce prior authorization criteria because the net price of these drugs would be reduced.

Drug manufacturers. Manufacturers would be required to pay larger Medicaid rebates on any of their products going through the accelerated approval pathway. Manufacturers would need to decide whether to bring their products to the market early under the accelerated approval pathway and incur the added cost of the increased rebate or to wait to complete Phase III trials and pursue the traditional approval pathway to pay the standard MDRP rebate.

A New Benefit for Cell and Gene Therapies

Cell and gene therapies are a subset of specialty drugs that are receiving significant attention due to their high costs and potential as durable (i.e., having long-term benefit) or curable treatments. For example, Zolgensma, a one-time intravenous infusion indicated to treat spinal muscular atrophy, has a list price of \$2.1 million.

Our pipeline analysis identified 45 cell or gene therapies indicated for pediatric populations and 61 therapies indicated for adults in Phase III or later

(e.g., a new drug application submitted). Because more than two out of every five children in the U.S. are Medicaid beneficiaries, high-cost pediatric products are of particular importance for Medicaid (MACPAC 2020b). While Medicaid is not likely to be the largest payer for gene and cell therapies indicated for adults, any use of these high-cost products may strain Medicaid budgets.

Cell and gene therapies tend to have extremely high up-front costs. Additionally, many of these therapies are indicated for conditions that affect a small population, creating uncertainty at the state and plan level about the number of individuals who might seek treatment in any given year. This combination of utilization uncertainty and high cost can cause significant budget volatility, which can be especially challenging for smaller states to manage using existing tools.

In addition to the high up-front costs, states have questions about the long-term benefit of covering these therapies. Because little data are available to assess the durability of these therapies, some stakeholders question whether these products will produce the long-term benefits suggested by manufacturers. Further, states recognize that if these products do deliver lasting benefits, they will be paying for treatments that may ultimately accrue benefits to other payers.

New benefit for cell and gene therapies

The TAP discussed how a new national drug benefit for cell and gene therapies could address the high up-front costs, budget volatility, and uncertainty in the long-term benefit that cell and gene therapies present. A new benefit would allow for new coverage, payment, or rebate requirements without disrupting the existing structure of the MDRP for all other outpatient drugs. One option would be to create a centralized, national coverage pool for these products. A federally administered program would allow standardization of coverage and payment rules across states and plans. Additionally, the model could be designed to ensure that coverage and payment rules are the same

regardless of setting. Currently, coverage, payment, and rebate requirements for drugs may differ depending on whether the drug is administered in the inpatient or outpatient setting and how payment is made.²¹

This model could be designed to address several concerns. For example, by increasing federal funding for these products and pooling patients nationally to increase utilization predictability, it could help address states' concerns about high up-front costs and budget volatility. It could also be designed with more flexible coverage than exists under current Medicaid drug coverage rules. A federal program would consolidate purchasing power, improving the ability to negotiate with manufacturers. Furthermore, the program could require Medicaid rebates or create new mandated rebates to guarantee a certain level of discount.

At this time, the Commission is not ready to make a recommendation on a new benefit for cell and gene therapies; rather, our goal for this chapter is to highlight the design choices and implications that would need to be considered.

Key design considerations

Establishing a new benefit for cell and gene therapies would require substantial statutory and regulatory changes at the federal and state levels. In thinking about the design options, policymakers need to consider both the overarching goals and the specific policy parameters, including which therapies to include and how to balance beneficiary access with efforts to control spending. In this section, we draw out these policy and design issues (Table 1.1).

TABLE 1-1. Design Options and Considerations for New Cell and Gene Therapy Benefit

Design element	Options and considerations
State participation	<ul style="list-style-type: none"> • Mandatory or optional for states • Multipayer model including Medicare and commercial insurers
Inclusion criteria	<ul style="list-style-type: none"> • Cover all cell and gene therapies or a subset of therapies • Base coverage on condition (i.e., all drugs for a certain condition, including drugs that are not cell and gene therapies) or only cover cell and gene therapies • Cover only cost of drug or all costs associated with administration of therapy (e.g., hospital stay)
Price	<ul style="list-style-type: none"> • Mandatory rebates similar to Medicaid Drug Rebate Program • Value-based price based on independent assessment of value • Outcomes-based contract • Combination of pricing models
Supply chain	<ul style="list-style-type: none"> • Incorporate a third party to manage and distribute the supply of the drug regardless of setting • Maintain rebate model to minimize supply chain disruptions
Scale and duration	<ul style="list-style-type: none"> • Demonstration versus permanent model • Permanent or temporary coverage in new benefit depending on amount of competition
Funding	<ul style="list-style-type: none"> • Increase federal funding • Require payer contributions if multipayer model

Source: NORC and MACPAC, 2021, findings from Technical Advisory Panel.

Below we discuss each design element and the potential considerations and tradeoffs of each option in more detail.

State participation. Participation in a new benefit for cell and gene therapies could be mandatory or optional for state Medicaid programs. Mandatory participation would create a larger risk pool, which would improve the ability to reduce up-front costs and smooth out budget volatility. Pooling risk across all states would reduce annual state or plan-to-plan variation in spending by creating a more predictable pool of treated patients. A bigger pool would also increase leverage to negotiate prices with manufacturers. However, mandatory

approaches to Medicaid policy inevitably lead to pushback from some stakeholders. If state participation was optional, it would be important to entice larger states into the pool to help spread risk and increase negotiating leverage. Large states have less incentive to opt into multistate pools because they tend to have more negotiating power than smaller states and are more likely to benefit from supplemental rebates. However, the new benefit would still be attractive to larger states if it included a pricing structure that provided a lower net price for cell and gene therapies that have limited or no competition for which manufacturers are not likely to provide meaningful supplemental rebates.

Another option would be to expand the benefit to include other payers, such as Medicare, the Department of Veterans Affairs, state or federal employees, and commercial insurers. A multipayer pool would help address state concerns about bearing the cost of gene and cell therapies that end up showing durability and prevent future disability and reduce long-term treatment costs that could accrue to another payer. Furthermore, it could increase coverage for patients to the extent that commercial insurers currently have an incentive to limit coverage for these products or to shift their members into Medicaid prior to treatment to avoid costs. A multipayer pool could reduce selection bias across payers and plans.

Inclusion criteria. Creating a new benefit would require decisions about which therapies would be included and for whom, and which additional services should be considered part of the benefit. For example, the benefit could be limited to those cell and gene therapies that are expected to have durable benefits versus those that may only have short-term benefits (e.g., blood transfusion). CMS or another federal entity would need to establish a process to define evidence of durability that would dictate inclusion in the model and adjust the criteria over time if necessary.

Therapies could also be selected for inclusion based on price. For example, the benefit could be structured to target only the highest-cost therapies (e.g., over \$1 million per treatment) or those with a certain amount of expected total spending (e.g., \$1 billion). However, a price or spending threshold could create a price floor, discouraging price competition if manufacturers target that amount when setting the list price to ensure inclusion in the new benefit.

A separate benefit for cell and gene therapies could create financial incentives for states to shift utilization toward those therapies, particularly if the benefit is fully federally funded. Condition-based inclusion criteria could address these concerns about encouraging use of a gene therapy over other alternatives. For example, the benefit could include all drugs for a certain clinical condition

(e.g., hemophilia). Even so, this could create difficult choices on which conditions to include. Some selection issues could be addressed by implementing strong clinical criteria to qualify for cell and gene therapy. To address beneficiary concerns about access, CMS and states could work with professional clinical societies or an independent expert panel (e.g., convened by the National Academies) to establish appropriate qualification criteria for treatment.

Many cell and gene therapy regimens include additional services, such as an inpatient hospital stay. The benefit could be structured to include only the cost of the drug or to cover a patient's entire cost of care. If the latter, additional decisions would be required to define the bundle of services provided as part of the normal course of treatment and whether payment should be standardized for all the other services.

Price. A key feature of a new cell and gene therapy benefit would be to allow for new payment and rebate models without disrupting the existing structure of the MDRP for all other outpatient drugs.

By consolidating gene and cell therapies into a separate drug benefit, the federal government would have increased negotiating leverage and may be able to obtain larger rebates. Under the current MDRP requirements, states argue that they lack the leverage to negotiate supplemental rebates on cell and gene therapies. These products do not have clinical alternatives and cannot be excluded from coverage. If these treatments are carved out and separated from the MDRP, manufacturers may be more likely to negotiate if all state volume is aggregated into a single pool. However, the federal government would only have significant negotiating leverage if exclusion of coverage is a possibility under the new benefit. Many stakeholders and beneficiary groups would have strong concerns about changing Medicaid rules to exclude coverage and limiting access to these treatments.

The program could also implement mandatory rebates similar to those in the MDRP to guarantee a

certain level of price reduction. These rebates could be set at a fixed percentage (e.g., a percentage of AMP) or could be tied to a mandatory outcomes-based contract so that the rebate would bring the net price down if the drug did not achieve the desired outcome. A uniform national benefit would streamline the development of an outcomes-based contract for the manufacturer, compared with negotiating with 51 separate state programs. If the benefit were extended to include other payers, collection of outcomes data could be simplified and beneficiary outcomes could be tracked more easily over time even if they switched payers or plans.

Alternatively, the federal government could set a value-based price, similar to a maximum allowable cost or upper payment limit. The value-based price would tie payment to an independent analysis of the product's value—a departure from current models, which anchor payment to the manufacturer-determined list price. The value assessment could come from an international pricing methodology or an organization such as the Institute for Clinical and Economic Review. Some stakeholders have concerns about using an international reference price and suggest that tying the price to an assessment from an organization based in the United States would be more acceptable because it would reflect existing U.S. priorities related to innovation and value. Other stakeholders would likely oppose this option entirely and argue that an upper price limit would disincentivize innovation and investment. Another concern is that setting a value-based price for Medicaid would cause manufacturers to raise prices in the commercial market. However, some argue that a federally supported value-based price could establish a strong benchmark that other payers would use for negotiation and that the ability to cost shift may be limited.

It is possible that such pricing models, while introducing new complexities, would not necessarily lead to a lower net price than is currently achieved through the existing MDRP. Combining new approaches with the existing minimum and inflationary rebate formulas of the MDRP could ensure that the new benefit would achieve a similar

or lower net price. For example, the total rebate for cell and gene therapies could be the lower of the MDRP rebate amount or the difference between AMP and a value-based price. Alternatively, the federal government could establish a mandatory outcomes-based contract for any drugs covered under the benefit to lower the price below the MDRP amount if the product does not achieve the anticipated outcome.

A new benefit separate from the MDRP also could be beneficial to manufacturers and commercial payers. For example, any best price established for the new benefit could be defined in a different way to better account for new pricing and rebate models than the MDRP currently allows. Separating cell and gene therapies into a new benefit could provide more flexibility for manufacturers and commercial payers to develop new models but limit any unintended consequences that a definitional change to best price under the MDRP could have on other drugs.

Supply chain. A new pricing model could disrupt the existing supply chain. Currently, states pay providers, not manufacturers, for drug acquisition costs. As a result, the federal government and the states would not set a value-based price for the product directly with the manufacturer. Rather, a value-based price would establish the payment to providers, who would then be forced to negotiate with manufacturers to ensure that their acquisition costs would be lower than the program payment rate. This traditional buy-and-bill process would put pressure on providers because manufacturers would not be required to sell their products to providers at the value-based price.

To address these concerns, a new benefit could incorporate a third party, such as a specialty pharmacy, to manage and distribute the supply of the drug, regardless of whether the therapy was administered in inpatient or outpatient settings. The specialty pharmacy model would reduce pressure on providers to acquire the product below the value-based price. But it would also eliminate existing revenue that providers make on the spread that can occur under the traditional buy-and-bill process.

A rebate model, particularly one like the MDRP, would not disrupt the existing supply chain. Providers could still operate under the buy-and-bill model, while the states would receive the rebate from the manufacturer to lower the net price.

Scale and duration. A new benefit for cell and gene therapies would require significant statutory changes, and it would require significant operational changes, time, and effort for drug manufacturers, states, and providers to implement. To minimize disruption and test whether the model works as intended, policymakers could start small, for example, as a demonstration, or only include a small number of therapies. A smaller scale would allow policymakers to learn from the model's outcomes in the early years and help them assess the overall effect on beneficiary access and other market dynamics.

Another consideration is whether this new benefit should permanently cover cell and gene therapies. The model could include a mechanism to determine whether at some point, coverage and payment for certain drugs would revert to prior models, for example, if generics were developed or if other sufficient competition became available. CMS would need to conduct routine evaluations of outcomes and beneficiary access, and assessments of whether drugs should move in or out of the benefit.

Funding. Financing for a new cell and gene therapy benefit could be shared between the federal government and states, as is currently the case in Medicaid, or fully financed by the federal government. Full federal funding would address the budget volatility within and across states. Furthermore, full federal funding could standardize coverage across all states, and could consolidate and streamline the implementation of new pricing structures (e.g., value-based pricing), financing models (e.g., pay over time), or outcomes-based contracts. However, this option would shift spending to the federal government and could increase incentives for states to try to shift utilization to cell and gene therapies from other potentially cheaper

treatments for which the state would share in the cost. Another option would be to increase the FMAP for the cell and gene therapy benefit. This option would help alleviate some of the budget pressure on the states but still leave some financial incentive for states to manage the use of these therapies.

Under a multipayer model, the financing could operate similar to a risk pool. Each payer could contribute to the financing by paying a fixed amount (e.g., per member per month). Similar to the Medicaid model, the federal government could contribute more funding to reduce the cost to each payer.

Stakeholder implications

Depending on how the new drug benefit is designed, it could have varying effects on beneficiaries, manufacturers, and providers.

Beneficiaries. If the model removed the coverage requirement, beneficiary access could be limited. Conversely, this model could improve access to gene and cell therapies by creating a unified approach to coverage and payment, rather than the variation in approaches that state Medicaid programs use today. Additionally, to protect beneficiary access, CMS could implement a strong patient appeal process to address concerns about patients' ability to navigate a federal program.

Manufacturers. Manufacturers would likely favor keeping the MDRP's mandatory coverage requirement to ensure drug access for Medicaid beneficiaries. While manufacturers have indicated that they are receptive to ways to better link drug price to effectiveness and value, they value the existing pricing model and would prefer incorporating outcomes-based contracts into the model to arrive at a value-based net price. In particular, they would not want to see a pricing model that penalizes cell and gene therapy manufacturers relative to manufacturers of traditional products. Similarly, they view a price ceiling or a rate-setting approach based on a third-party evaluation as politically untenable, but

they could see using a third-party evaluation as a starting point for negotiation. If the new benefit for cell and gene therapies allowed for more restrictive coverage or lower net prices than under the MDRP, manufacturers could be concerned that the coverage or pricing models would eventually be expanded to other drugs as a way to reduce Medicaid costs.

Providers. Because cell and gene therapies are administered by providers, concern could arise that a new benefit could increase the administrative burden by separating the authorization processes for drugs and any ancillary services. However, given that the process for obtaining approval for a cell or gene therapy already has many hurdles, an additional prior authorization requirement would not necessarily affect physician decisions.

Providers may also have concerns that this model would require separate claims systems for the drug and the associated medical services, thus fragmenting data that would be needed to conduct retrospective reviews. This fragmentation in coverage and payment systems may already be happening to some extent in states that either carve out certain therapies from managed care contracts or separate payment for the drug from the associated medical services in the inpatient setting. It would be important to have integrated data systems so providers and researchers would have a complete view of the patient's medical history.

Another concern is the potential for lost revenue if the buy-and-bill process was eliminated. However, most cell and gene therapies currently are distributed through specialty pharmacies or a select number of centers of excellence, so the buy-and-bill process is not typical for gene and cell therapies at this point and may not be a major source of revenue for most providers.

Consideration for a National Registry

One limitation of models that seek to link a drug's price to its effectiveness and value is that they require data collection to demonstrate that specific appropriate and meaningful outcomes have been achieved. The TAP discussed at length the need for improved outcomes data, and the administrative burden and costs of data collection. Such challenges concern all payers but may be particularly notable for Medicaid due to the churn of beneficiaries in and out of the program, as well as the potential need to coordinate data collection across several different Medicaid managed care plans. Given the significant amount of public funding being used to cover specialty drugs in Medicaid, the TAP suggested that the federal government consider creating a national data registry to track outcomes for patients taking these products. Such data could be used to support coverage and payment decisions. Participants suggested that CMS could work with the FDA and the National Institutes of Health to develop a national registry to collect and share data with states and Medicaid managed care plans; the registry could also be expanded to include other payers.

A national registry could have several benefits. It could provide real-world evidence to the FDA and payers for multiple purposes, including postmarketing evaluation of clinical efficacy and safety of accelerated approval drugs, value assessments of cell and gene therapies, and long-term outcomes tracking as beneficiaries move across states and Medicaid managed care plans, or to other payers, such as Medicare or private insurance. A national registry could also be beneficial to drug manufacturers as it could centralize outcomes data and allow for greater standardization and adoption of outcomes-based contracts. In addition, it could reduce the cost of postmarketing clinical trials if the FDA incorporated real-world evidence from the registry data into its evaluation of clinical efficacy and safety.

Next Steps

The Commission will continue to focus attention on the merits of a new benefit for cell and gene therapies, including how to address tradeoffs. For example, the Commission will want to gather more evidence and input on the strengths and weaknesses of the various options that could be used to establish a net price for such a benefit. In doing so, we plan to reach out to various stakeholders for input on the framework and monitor the development of new proposals for alternative coverage or payment models for cell and gene therapies.

Endnotes

¹ There is no single definition of specialty drugs, and researchers and industry stakeholders may use different criteria in identifying specialty drugs. Some rely solely on price, while others include other characteristics, such as treating a chronic, complex, or rare disease, requiring special handling in the supply chain, being initiated or maintained by a specialist, being administered by a professional, or being distributed through non-traditional channels such as a specialty pharmacy (CBO 2019).

² For its analysis, CBO identified the specialty drugs that were on the market in 2015 using a definition developed by IQVIA (formerly known as IMS Health). This definition encompasses drugs that treat a chronic, complex, or rare condition and that have at least four of the following seven characteristics: (1) cost at least \$6,000 per year, (2) be initiated or maintained by a specialist, (3) be administered by a health care professional, (4) require special handling in the supply chain, (5) be associated with a patient payment assistance program, (6) be distributed through non-traditional channels (such as a specialty pharmacy), or (7) require monitoring or counseling either because of significant side effects or because of the type of disease being treated. The list of specialty drugs on the market in 2015 was purchased from IQVIA and is proprietary (CBO 2019).

³ In addition to executing a Medicaid drug rebate agreement as a condition for Medicaid coverage of their products, drug manufacturers must enter into an agreement that meets the requirements of Section 340B of the Public Health Service Act (P.L. 102-585) and a master agreement with the Secretary of Veterans Affairs (§ 1927(a)(1) of the Act). Additionally, the manufacturer must enter into a Medicaid drug rebate agreement in order for payment to be made under Medicare Part B. A drug not covered under a rebate agreement may be eligible for federal Medicaid funding in limited circumstances if the state has determined that the drug is essential to the health of its beneficiaries.

⁴ A medically accepted indication means any use for a covered outpatient drug that is approved under the Federal Food, Drug, and Cosmetic Act (P.L. 75-717) or that is supported by one or more citations included or approved for inclusion in one of the following three compendia: American Hospital Formulary Service Drug Information, United States Pharmacopeia-Drug Information, or the DRUGDEX Information System (§ 1927(k)(6) of the Act).

⁵ A drug manufacturer must have a signed Medicaid drug rebate agreement in place in order for its products to be covered by Medicaid. If a manufacturer does not have a rebate agreement with the Secretary, a state does not have to cover that manufacturer's products until the rebate agreement is effective.

⁶ For Medicare Part D formularies, each drug category or class must include at least two drugs (regardless of the classification system utilized). Part D plan formularies must include all or substantially all drugs for the following six protected classes: immunosuppressants (for prophylaxis of organ transplant rejection), antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics (CMS 2016a). Exchange plans must cover one drug in every United States Pharmacopeia category and class, or the same number of drugs in each category and class as the state benchmark plan (45 CFR 156.122(a)(1)).

⁷ The covered outpatient drug rule finalized in 2016 includes a separate definition of AMP for the so-called 5i drugs—inhalation, infusion, instilled, implanted, or injectable drugs. These drugs are not generally sold through the same distribution channels as other drugs, so the AMP for 5i drugs includes sales of a type not included in AMP calculations of non-5i drugs.

⁸ Generally, an innovator drug is a drug produced or distributed under a new drug application approved by the FDA. Single source drugs are innovator drugs manufactured by only one company and innovator multiple source drugs are innovator drugs that have at least one generic equivalent available. Non-innovator multiple source drugs are multiple source drugs that are not innovator drugs—generally, these are drugs that have been approved by the FDA under an abbreviated new drug application.

⁹ For blood clotting factor drugs and drugs approved by the FDA exclusively for pediatric indications, the rebate percentage is 17.1 percent of AMP, instead of 23.1 percent of AMP.

¹⁰ Best price excludes certain governmental payers, such as the Indian Health Service, Department of Veterans Affairs, Department of Defense, Public Health Service (including 340B), Federal Supply Schedule, and Medicare Part D plans.

¹¹ The baseline AMP is the AMP during the quarter before the Medicaid Drug Rebate Program was started or, for new drugs, the first full quarter after the drug's market date. For generic drugs marketed on or before April 1, 2013, the baseline AMP is equal to the AMP for the third quarter of 2014, and the baseline CPI-U is the CPI-U for September 2014. For generic drugs marketed after April 1, 2013, the baseline AMP is equal to the AMP for the fifth full calendar quarter after which the drug is marketed as a drug other than a brand drug, and the baseline CPI-U is equal to the CPI-U for the last month of the baseline AMP quarter (CMS 2016b).

¹² In accordance with Section 2501(c) of the Patient Protection and Affordable Care Act (ACA, P.L. 111-148, as amended), 24 states—Arizona, Arkansas, California, Delaware, Florida, Illinois, Iowa, Kansas, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Nebraska, New Hampshire, New York, North Dakota, Ohio, Oregon, Pennsylvania, Texas, Virginia, Washington, and West Virginia—are expanding supplemental rebate collections to include drugs dispensed to beneficiaries who receive drugs through a managed care organization (MCO). Minnesota limits its collection of supplemental rebates for MCO enrollees to direct-acting antivirals for the treatment of hepatitis C (CMS 2020).

¹³ Phase I trials are conducted in a small group of people to determine safety (e.g., dosing range) and identify side

effects. Phase II trials involve a few hundred people with the disease or condition for which the drug is being developed and are designed to test for efficacy and additional safety data. The size of the trial usually is not large enough to show whether the drug is beneficial. Phase III trials are large studies of people with the disease or condition and are designed to demonstrate the efficacy of the drug compared with commonly used treatments and to monitor for adverse reactions. The FDA grants approval after the successful completion of Phase III trials. Phase IV trials include postmarketing requirements or commitments carried out after the drug has been approved by the FDA (FDA 2018).

¹⁴ Oklahoma received a state plan amendment in 2018 to allow the state to negotiate outcomes-based contracts with manufacturers through a supplemental rebate agreement. In 2019, Oklahoma's Medicaid pharmacy director stated that the agency dedicated an enormous amount of time to enter into contracts, meeting with 27 companies (more than three meetings with most of the companies), only to successfully negotiate four contracts. In addition, she acknowledged that defining outcomes that are sufficient indicators of efficacy has been a challenge. The manufacturer frequently wanted to use a clinical or laboratory measure that is not available in the state's claims data (Murad 2019).

¹⁵ In order to qualify for accelerated approval, a drug must treat a serious condition, generally provide a meaningful advantage over available therapies, and demonstrate an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint) (FDA 2014).

¹⁶ Section 506(c)(2) of the Federal Food, Drug, and Cosmetic Act states that approval under the accelerated approval pathway may require the sponsor to conduct appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit. This could allow the FDA to grant accelerated approval without requiring a confirmatory trial. However, the FDA, through regulations and guidance, has indicated that accelerated approval will be subject to the requirement that the manufacturer study the drug further to verify the clinical benefit (21 CFR 314.510, 21 CFR 601.41, FDA 2014). The

confirmatory trial does not have to be a separate trial and may be a continuation of an ongoing trial. We are not aware of any example where accelerated approval was granted without a requirement for a confirmatory trial.

¹⁷ The manufacturer has requested a hearing, after which the FDA commissioner will decide whether to withdraw approval of Makena and its approved generic equivalents. Makena and its approved generic equivalents will remain on the market until the manufacturers decide to remove the drugs or the FDA commissioner mandates their removal.

¹⁸ The FDA may grant accelerated approval for new indications after a drug has been initially approved (including under traditional approval). Because Medicaid rebates are determined at the national drug code (NDC) level and pricing generally does not differ based on indication, the increased rebate would not apply if the drug has received traditional approval for at least one indication for that particular NDC.

¹⁹ The FDA uses the terms traditional, full, and normal approval interchangeably when discussing the conversion from accelerated approval. The conversion does not require another new drug application (NDA) but is typically executed as a supplement NDA that indicates the manufacturer has fulfilled its commitment under 21 CFR 314.510 or 21 CFR 601.41 to verify the clinical benefit.

²⁰ In 2017, Massachusetts submitted a Section 1115 demonstration waiver that explicitly requested authority to not cover some drugs granted accelerated approval because they “have not yet demonstrated clinical benefit” and “can be particularly costly” (CMS 2017). This portion of the Section 1115 demonstration waiver request was denied by CMS in 2018 (CMS 2018b). In 2019, Tennessee submitted a Section 1115 demonstration waiver amendment that requested authority to implement a closed formulary and specifically highlighted accelerated approval drugs as an area where it wanted flexibility “to exclude these new drugs from its formulary until market prices are consistent with prudent fiscal administration or the state determines that sufficient data exist regarding the cost effectiveness of the drug” (CMS 2019). Earlier this year, CMS approved the state’s request to implement a closed formulary while still receiving the MDRP rebates as part of the state’s modified block grant financing structure. This is the first time CMS has allowed a state to exclude coverage and still receive the MDRP rebates (CMS 2021).

²¹ The definition of covered outpatient drugs under the MDRP excludes drugs that are billed as part of a bundled service within certain settings (e.g., drugs provided as part of a clinic visit or hospital stay and paid for as part of those services (§ 1927(k)(3) of the Act). This means that if a drug is provided as part of services received in one of the settings listed in the statute and is paid as part of those services (i.e., there is not direct payment for the drug), it is not subject to a rebate. However, if a state authorizes and makes a direct payment for the drug separately from the service in one of those settings, it can claim a rebate for that drug. Because certain cell and gene therapies can be administered in both the inpatient and outpatient settings, the coverage requirements and applicability of Medicaid rebates under the MDRP may be different depending on the setting and payment methodology.

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Commission Vote on Recommendations

In MACPAC’s authorizing language in Section 1900 of the Social Security Act, Congress requires the Commission to review Medicaid and CHIP policies and make recommendations related to those policies to Congress, the Secretary of the U.S. Department of Health and Human Services, and the states in its reports to Congress, which are due by March 15 and June 15 of each year. Each Commissioner must vote on each recommendation, and the votes for each recommendation must be published in the reports. The recommendations included in this report, and the corresponding voting record below, fulfills this mandate.

Per the Commission’s policies regarding conflicts of interest, the Commission’s conflict of interest committee convened prior to the vote to review and discuss whether any conflicts existed relevant to the recommendations on high-cost specialty drugs. It determined that, under the particularly, directly, predictably, and significantly standard that governs its deliberations, no Commissioner has an interest that presents a potential or actual conflict of interest.

The Commission voted on Recommendations 1.1 and 1.2 on April 9, 2021.

High-Cost Specialty Drugs

1.1 Congress should amend Section 1927(c)(1) of the Social Security Act to increase the minimum rebate percentage on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased rebate percentage would apply until the manufacturer has completed the postmarketing confirmatory trial and been granted traditional FDA approval. Once the FDA grants traditional approval, the minimum rebate percentage would revert back to the amount listed under Section 1927(c)(1)(B)(i).

Yes: Bella, Brooks, Burwell, Carter, Cerise, Davis, Douglas, George, Gordon, Gorton, Lampkin, Milligan, Retchin, Scanlon, Szilagyi, Weno

16	Yes
1	No

No: Barker

1.2 Congress should amend Section 1927(c)(2) of the Social Security Act to increase the additional inflationary rebate on drugs that receive approval from the U.S. Food and Drug Administration (FDA) through the accelerated approval pathway under Section 506(c) of the Federal Food, Drug, and Cosmetic Act. This increased inflationary rebate would go into effect if the manufacturer has not yet completed the postmarketing confirmatory trial and been granted traditional FDA approval after a specified number of years. Once the FDA grants traditional approval, the inflationary rebate would revert back to the amount typically calculated under Section 1927(c)(2).

Yes: Bella, Brooks, Burwell, Carter, Cerise, Davis, Douglas, George, Gordon, Gorton, Lampkin, Milligan, Retchin, Scanlon, Szilagyi, Weno

16	Yes
1	No

No: Barker