AMCP

# FORMAT 6.0

## Format for Formulary Submissions

**Guidance on Submission of Post-Approval and Pre-Approval Clinical and Economic Information and Evidence**

**Select Provisions for Public Comment**

AMCP
Optimizing medicine.
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**REQUEST FOR PUBLIC COMMENT**

**Date:** March 17, 2026
**Version:** 6.0

**Comment Period Closes:** April 22, 2026

# AMCP Format for Formulary Submissions

*Guidance on Submission of Pre-approval and Post-approval Clinical and Economic Information and Evidence*

## Version 6.0 Revisions — Select Provisions for Public Comment

## Introduction

A revision is being proposed to the AMCP Format for Formulary Submissions, version 6.0, specifically in the following areas:



## Purpose of This Public Comment Period

AMCP recognizes that stakeholders across the pharmaceutical industry, including pharmaceutical manufacturers, payers, academics, consultants, and professional associations, use the Format in varying ways. We invite feedback during this public comment period to ensure the needs of all stakeholders continue to be met as updates are released.

AMCP developed the AMCP Format as a template and guidance for developing dossiers. Please consider if the proposed updates will allow the Format to continue to serve this purpose and assist you in your use of the Format and/or dossiers.

## Current Format version 5.0

The link to the current version of the Format (5.0) is provided below for reference. Proposed changes are described as they relate to the current version of the Format.

- **Version 5.0:** https://www.amcp.org/sites/default/files/2024-04/AMCP-Format-5.0JMCP-web_0.pdf

## How to Submit Comments

AMCP welcomes comments from all stakeholders. Comments should be submitted by **Wednesday, April 22, 2026** via the following method(s):

- **Online:** https://www.surveymonkey.com/r/38CMFPL
- **Email:** profaff@amcp.org

## Timeline

- **Public comment period opens:** 3/17/2026
- **Public comment period closes:** 4/22/2026
- **Review and adjudication of comments:** May 2026
- **Anticipated publication of final version:** October 2026

## Contact Information

For questions regarding this public comment period, please contact:

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# General Updates

The following general updates are proposed to address questions that have come up since the publication of Format v5.0 regarding artificial intelligence, how soon dossiers should reflect updates from the new version of the Format after publication, and additional guidance on products approved or undergoing review through the Accelerated Approval pathway.

## Role of the AMCP Format

To address the role of artificial intelligence in dossier development, the following statement was added:

> The authors of dossiers may choose to use artificial intelligence (A.I.) as a writing and editing assistant to organize material, summarize information and suggest ways to streamline and rephrase content. It is recommended that a qualified individual validate and finalize the dossier information.

## Updating Dossiers for Approved Products

To address questions that have been received in the past regarding Format adoption, the following paragraph was added:

> If a new Format is published by AMCP, manufacturers are encouraged to adopt the updated Format when appropriate. For new dossiers, the adoption of the updated Format should occur with the initial submission. For existing dossiers, adoption should take place at a logical time, such as during an update or when new data becomes available.

## Section 2.1A Product Information

To further elaborate on FDA designations, the following highlighted language was added. Text that is not highlighted is included for context. Similar language has also been added to 2.1C, number 11.

> The following are the components that may be included (per FDA Final Guidance, the PIE Act, and AMCP Format recommendation): ...
>
> 8. Information regarding FDA expedited approval, priority review, breakthrough therapy, accelerated approval or fast track designation. For products with special FDA designations (e.g., fast track, orphan designation, breakthrough) provide rationale why these designations were sought and granted. Specifically for products going through the Accelerated Approval pathway, describe the surrogate or intermediate endpoint that will be evaluated in clinical trials (e.g., has surrogate or intermediate endpoint been validated, used in other clinical development programs) and the timeline for completion of confirmatory trials, if known.

# Biosimilars

Guidance on biosimilar dossiers has been proposed in the Special Content Considerations section and in the newly added Appendix E.

### Special Content Considerations > Biosimilars

| Current language in Format, v. 5.0 | Proposed language in Format, v. 6.0 |
|---|---|
| The FDA has provided guidance on the analyses and testing that are required to demonstrate biosimilarity and interchangeability. Companies that develop biosimilars should incorporate these considerations into dossiers to allow health care decision-makers to fully evaluate these products. | The FDA has provided guidance on the analyses and testing that are required to demonstrate biosimilarity and interchangeability. To expedite the review process, it is recommended that companies who develop biosimilars follow the biosimilar submission guidance found in Appendix E rather than completing a full dossier. |

Underlined red text has been removed. Underlined green text has been added.

## Appendix E: Biosimilar Submission Guidance

The creation of and subsequent review of AMCP dossiers is a resource-intensive process. Given the significant overlap in material between an innovator and biosimilar dossier, it is recommended that companies who develop biosimilars follow the biosimilar submission guidance below rather than completing a full dossier. This guidance highlights key attributes of importance in the formulary decision-making process.

| Type of Information | Description of Information |
|---|---|
| Prescribing information | Include a hyperlink to the current prescribing information. |
| FDA Approved indications | Does this biosimilar have the same FDA approved indications as the reference product? If not, detail the differences. |
| Approvals outside of the US | List the countries outside of the U.S., year of approval, and indications that this biosimilar has, if any. |
| Manufacturer | List the manufacturer of the biosimilar along with any affiliations this manufacturer has to other manufacturers. |
| Country of Origin | In which country(s) is the biosimilar manufactured and packaged? |
| Cost per formulation | List the NDC(s), description of NDC(s) including dosage forms and strengths, and current WAC price associated with the NDC(s). |
| Maximum Fair Price status of innovator | Has the innovator been negotiated through the Inflation Reduction Act process? If no, when will it be first eligible for negotiation? |
| Interchangeability | Is this product an interchangeable biosimilar? |
| Distribution | Is this biosimilar broadly available, available only via a limited distribution network, or exclusively available to one company under a private label agreement? |
| List of studies submitted to the FDA | Provide study name, reference, and hyperlink along with a summary of whether approval of the biosimilar was supported by direct or extrapolated evidence. |
| Distinguishing attributes | List any product attributes that differ from the reference product that are not accounted for in the fields above. |
| Other key information | This section is intended for distinguishing information not otherwise listed above. |

# Gene and Cell Therapies

Guidance for dossiers for gene and cell therapies has been proposed in the following sections.

## Special Content Considerations > Gene and Cell Therapies

Gene therapies and cell therapies represent a rapidly evolving category of medical products that introduce unique clinical, operational, and economic considerations for health care decision-makers (HCDMs). These therapies may involve the modification of genetic material or the administration of living cells to prevent, treat, or potentially alter the course of disease. Gene and cell therapies may be used as stand-alone interventions or in combination with other treatments and may be administered as a one-time or limited-duration therapy.

While gene and cell therapies are regulated through established FDA pathways, their development, administration, and evidence generation may differ from traditional pharmaceuticals. These therapies are often designed to address serious or rare conditions, may target narrowly defined patient populations, and may rely on specialized diagnostic testing, manufacturing processes, and treatment settings. As a result, additional information beyond that typically included for conventional drug products may be needed to support formulary, coverage, and reimbursement decision-making.

The role of the AMCP Format for gene and cell therapies is the same as for other medical products: to convey evidentiary needs and to support consistent, transparent communication of clinical and economic evidence. The goal of the dossier is to enable HCDMs to evaluate the benefit–risk profile, place in therapy, and potential value of these therapies in the context of available alternatives and system-level considerations.

Because of the distinct characteristics of gene and cell therapies, manufacturers are encouraged to clearly describe relevant attributes of the product and its use, including, where applicable:

- Whether the therapy is a gene therapy, cell therapy, or a combination of both, and whether it is autologous or allogeneic
- The intended mechanism of action and expected durability of effect, including the biological rationale supporting long-term outcomes
- Patient identification and selection criteria, including any required genetic, biomarker, or diagnostic testing
- Requirements for product handling, manufacturing, chain-of-custody, administration, and associated REMS programs
- Requirements for additional drugs on hand

- Site-of-care considerations, such as the need for inpatient versus outpatient administration, specialized facilities, trained personnel, certification programs or supportive care
- Monitoring and follow-up expectations, including long-term safety surveillance or registry participation

These considerations may be addressed within existing sections of the dossier. Product characteristics and administration requirements may be described in **Product Information and Disease Description**, while clinical evidence, including pivotal trials and supporting studies, should be presented in **Clinical Evidence** sections. Information related to long-term follow-up, real-world evidence generation, and uncertainty in outcomes may be included in **Additional Supporting Evidence**, as appropriate.

HCDMs require meaningful evidence to evaluate gene and cell therapies, including data supporting clinical benefit, safety, and durability of response. At the time of regulatory approval, evidence may be limited by small study populations, single-arm trial designs, surrogate endpoints, or limited duration of follow-up. Manufacturers should present the highest-quality evidence available and clearly distinguish observed outcomes from projected or modeled long-term effects. Plans for ongoing evidence generation, such as post-marketing studies or patient registries, should be described when available. At a minimum, a description of required confirmatory trials should be provided if the therapy is granted Accelerated Approval.

Economic considerations for gene and cell therapies may differ from those of therapies intended for chronic administration. Upfront costs, timing of expenditures relative to realized benefits, and uncertainty regarding long-term outcomes may have important implications for affordability and budget impact. The AMCP Format does not prescribe specific economic models or payment approaches for these therapies but encourages transparent communication of assumptions, time horizons, and limitations used in economic analyses.

As with other products addressed by the AMCP Format, dossiers for gene and cell therapies should be viewed as living documents that evolve as new evidence becomes available. Clear, objective presentation of evidence and ongoing dialogue between manufacturers and HCDMs are essential to support informed, population-based health care decision-making for these therapies.

## 2.1B Product Information

Under section 2.1B Product Information, no new information was added within the digital therapeutics subsection; however, this section has been given its own number (2.1.**1**B) so that a new section (2.1.**2**B) may be added for Gene and Cell Therapies, which includes the language and table (Table 2.1.2B) below. The Product Comparison subsection has been renumbered to 2.1.**3**B.

For gene and cell therapies, the Product Information section (2.1) should provide sufficient detail to allow health care decision-makers (HCDMs) to understand the key attributes of the product and the requirements for its appropriate use. While many standard elements of product information apply, additional context may be necessary due to the unique scientific, manufacturing, and administration characteristics of these therapies.

For gene and cell therapies, complete all relevant product description information in addition to the Table of Highlights for Gene and Cell Therapies (Table 2.1.2B).

**Table 2.1.2B: Table of Highlights for Gene and Cell Therapies**

| Type of Information | Description of Information |
|---|---|
| **Product classification** | Identify whether the product is a gene therapy, cell therapy, or combination product. Indicate whether the therapy is autologous or allogeneic, if applicable. |
| **Mechanism of action** | Describe the intended biological mechanism, including genetic modification, cellular activity, or functional correction. Include information on persistence, integration, or expected duration of biological activity when known. |
| **Intended treatment paradigm** | Describe whether the therapy is intended as a one-time administration, time-limited course, or repeatable therapy. Indicate whether retreatment has been studied, is anticipated, or may be considered based on durability of response. |
| **Target population** | Describe the indicated patient population, including any relevant genetic, biomarker, or diagnostic criteria used to identify eligible patients. |
| **Required diagnostic or genetic testing** | Identify required or recommended tests used for patient identification, eligibility confirmation, or treatment planning. |

| | |
|---|---|
| **Pre-treatment or conditioning requirements** | Describe any required or recommended preparatory regimens, such as conditioning chemotherapy, immunosuppression, or supportive care, including the toxicity profile and resource implications of these regimens when relevant to system planning. |
| **Route and method of administration** | Describe the route of administration and method of delivery (e.g., intravenous infusion, direct tissue administration). |
| **Site-of-care requirements** | Identify the care setting required for administration (e.g., inpatient, outpatient, specialty center) and any facility certification or accreditation requirements. |
| **Personnel and training requirements** | Describe any specialized training, credentialing, or expertise required for clinicians or staff involved in administration and monitoring. |
| **Manufacturing and logistics considerations** | Summarize relevant manufacturing attributes, including patient-specific production (if applicable), timelines, storage conditions, and transportation requirements. |
| **Chain-of-identity and chain-of-custody** | Describe processes used to ensure correct product–patient matching throughout manufacturing, delivery, and administration. Identify any requirements for vein-to-vein coordination or time-sensitive logistics, when applicable. |
| **Safety considerations requiring extended monitoring** | Identify known or potential risks that require ongoing or long term monitoring beyond standard post-administration observation. |
| **Post-Treatment requirements, Long term follow-up expectations** | Describe any required post-treatment procedures. Describe recommended or required duration and type of follow-up, including post-marketing studies or registry participation, if applicable. |
| **Regulatory designations** | List relevant FDA designations (e.g., orphan drug, breakthrough therapy, accelerated approval, regenerative medicine advanced therapy) and dates, if applicable. |
| **Information gaps or uncertainties** | Identify key areas where evidence is limited or evolving at the time of submission and how these uncertainties are being addressed or monitored. |

## 3.3A, 3.3B, and 3.3C Gene and Cell Therapies

The following subsection has been added under Section 3.0 Clinical Evidence in Sections A (Unapproved Product Dossiers), B (Approved Product Dossiers), and C (Unapproved Use Dossiers). Please note that text that is highlighted in yellow has only been added to 3.3**B**.

For gene therapies and cell therapies, the clinical evidence section should present the full body of available evidence supporting the proposed use of the product in a clear, balanced, and transparent manner. As with other medical products, manufacturers should include all relevant studies that meaningfully contribute to understanding clinical benefit and safety, recognizing that the nature of available evidence may differ from that of therapies intended for chronic administration.

Clinical development programs for gene and cell therapies may involve small or highly selected patient populations, single-arm trial designs, adaptive or innovative study methodologies, surrogate or intermediate endpoints, and limited duration of follow-up at the time of regulatory review. When such designs are used, manufacturers should clearly describe the rationale for the chosen approach, the implications for interpretation of clinical outcomes, and the appropriateness of any comparator groups or external controls utilized.

Manufacturers are encouraged to clearly distinguish between:

- **Observed clinical outcomes** measured directly within clinical trials or other studies, and
- **Projected or anticipated long-term outcomes** that are based on biological plausibility, modeling, historical controls, or extrapolation beyond the observed follow-up period.

When long-term benefit or durability of effect is a key aspect of the therapy's value proposition, the biological rationale supporting durability should be described, along with any available empirical evidence. Limitations related to follow-up duration, uncertainty in long-term outcomes, and variability in response across patients should be transparently presented.

Safety evidence for gene and cell therapies may require particular attention due to the potential for delayed or long-term adverse effects, including late-onset toxicities and secondary malignancies where relevant. Manufacturers should summarize known and potential risks identified in clinical trials, including serious or rare adverse events, and describe ongoing or planned monitoring strategies, such as long-term follow-up studies or patient registries, when applicable.

Where available, real-world evidence and post-marketing data should be incorporated as they become available to complement clinical trial findings, to support accelerated approval indications, and to inform understanding of effectiveness, safety, and durability in broader patient populations. The methods used to generate and analyze such evidence should be described, and any limitations should be acknowledged.

Given the evolving nature of evidence for gene and cell therapies, dossiers should be updated as new clinical data emerge, including results from longer-term follow-up studies, expanded patient cohorts, or real-world use, or findings from confirmatory studies for products approved through the Accelerated Approval pathway. Consistent with the AMCP Format's principles, the clinical evidence section should support informed evaluation by HCDMs by clearly presenting the strength, limitations, and relevance of the available evidence.

## 5.6A, 5.7B, 5.7C Gene and Cell Therapies

The following subsection is proposed to be added to section 5.0 Additional Supporting Evidence. The existing "Other Evidence or Information" subsections will be renumbered to 5.7A, 5.8B, and 5.8C, respectively.

Additional evidence may also address operational and system-level considerations that affect the real-world use of gene and cell therapies. Such considerations may include requirements for specialized treatment centers or centers of excellence, which can influence geographic access to care and may result in disparities related to patient location, referral pathways, or health system infrastructure. Manufacturers may describe how site-of-care requirements, provider training, and certification programs affect patient access and the capacity of health systems to deliver and support these therapies.

Supporting evidence may also address health system readiness and capacity for treatment delivery and follow-up, including care coordination across providers, availability of specialized personnel, and the resources required to support extended monitoring or long-term follow-up. Where relevant, information on system-level impacts such as inpatient versus outpatient resource use, staffing demands, or coordination with specialty pharmacies or transplant services may be included.

In addition, manufacturers may describe patient and caregiver experience associated with gene and cell therapies, including treatment burden, follow-up requirements, and potential impacts on quality of life. This may include discussion of financial toxicity for patients and payers, such as out-of-pocket costs, benefit design considerations, travel or

lodging requirements, loss of income during treatment and recovery, caregiver burden, and the timing of costs relative to clinical benefit. When available, supporting evidence or real-world experience related to these factors may help contextualize access, affordability, and overall value for health care decision-makers.

# 4.0B Economic Value and Modeling Report

As section 4.0B has been extensively revised, the entirety of this section is copied below for public comment. Updates are highlighted, including new text and language that has been moved (e.g., from on section to another or within the same section). The recommended length of Section 4.0B remains unchanged at 12 pages (maximum 20) for each model.

## 4.1B Modeling Overview

This section presents an overview of the rationale, approach, and methods for developing economic models. The intent of modeling is to quantify for the HCDM the economic value and budgetary impact of the product. The AMCP Format provides recommendations for the types of evidence and reporting formats that are likely to be useful for HCDM. However, the need for flexibility is recognized by AMCP. Manufacturers are encouraged to align with the recommendations below to the extent practicable.

### 4.1.1B Use of Modeling for Decision-Making

Available data on the clinical benefits and harms and economic impact of the product under consideration are provided in Sections 3.0B and 5.0B of the Approved Product Dossier and are the core of evidence-based decision-making. Source data for models pertaining to the clinical benefits of the product should be discussed in Section 3.0B, whereas Section 5.0B should discuss other data derived from external sources such as clinical practice guidelines, prior HTAs, and real-world evidence which may also provide source information for economic modeling.

Because of complexity and the uncertainty of underlying assumptions, models can be perceived as biased or unreliable.

Important limitations of economic models for decision-making include:

1. RCTs may not include all relevant comparator interventions.
2. The duration of follow-up in RCTs may be limited.
3. RCTs may not have collected all necessary data for economic evaluation.
4. Patient populations in RCTs may not be representative of plan populations or patient subgroups.
5. Safety data may be limited or from disparate sources.
6. Health care costs may not be generalizable across HCDMs.
7. Real-world evidence may be less precisely collected than RCT data, with potential discrepancies in data based on the data source (medical study registry data vs. pharmacy claims).

The AMCP Format has been developed to help address these limitations by providing overall guidance for transparent model development and reporting to improve acceptability.

### 4.1.2B Types of Models

Typically, the economic modeling section will include both cost-effectiveness and budget impact analyses. Other types of data may also be included to explain the economic aspects of the therapy; for example, to supplement internal models that may be developed by HCDMs.

#### Cost-effectiveness Models

Cost-effectiveness models based on decision analytics can provide insights into the longer-term value of health care products in comparison to products in its class or other health care interventions for a target population. Typically, they incorporate evidence on the usual disease course, the medical costs of care across the disease continuum, the relative and absolute risk reductions offered by the product, quality-of-life effects, and the costs of the product and associated health care utilization. Key aspects of cost-effectiveness models include the evaluation timeframe and perspective, and robust sensitivity analyses examining uncertainty in the model's parameters.

#### Budget Impact Models

Budget impact analyses address the question, "Is the technology affordable to the health system?" A budget impact model estimates the financial consequences associated with utilizing a new product at various levels of uptake and incorporates projected changes in the utilization of other health care resources." Budget impact models are not intended to establish the overall value of health care technologies because they do not follow treated cohorts over time to include the full long-term effects of the technology on clinical and patient outcomes; rather, their purpose is to estimate short-term affordability. These models, as defined here, typically estimate the target population for treatment, drug/product costs, health care cost offsets, and adverse event costs, as well as the expected utilization in the health care system, to derive PMPM and overall cost projections.

## 4.2B Cost-Effectiveness Analysis

### 4.2.1B Approach and Framework

#### Guidelines

Cost-effectiveness models can be relatively complex and should follow the broad guidance in this section, as well as recommendations published by the Second Panel on Cost-Effectiveness in Health and Medicine, the ISPOR / Society for Medical Decision Making (SMDM) Modeling Good Research Practices Task Force, and other seminal guidance.[42,65-70]

Explanations of the model should include the following:

1. Disease or condition addressed by the product, the patient population presumed in the model, the natural history and clinical course, and outcomes assessed. When a product is intended for treatment of more than one disease or indication, its cost-effectiveness should be modeled separately for each treatment population.
2. Relevant treatment options and the treatment process for each option—preferably based on treatment guidelines or actual practice and ideally using standard of care therapy as the comparator.
3. Costs of the products included in the model and medical resources consumed over the model's time horizon.
4. Occurrence rate and costs associated with adverse events, and frequency of and costs of monitoring for both therapeutic effect and safety.
5. Outcomes of therapy for the product and comparator(s) over the model's time horizon.
6. Cost and outcomes analysis presented in cost/consequences tables and as incremental cost-effectiveness ratios.
7. Details of model assumptions, and sensitivity analyses addressing key uncertainties.

Clarity and transparency of presentation are a necessity. This includes providing a high-level overview of the model structure, components, and outputs. All calculations should be explained in a simple, straightforward manner to allow a non-health economist to comprehend the analysis. The information and references should be accessible in the report format, as well as shown directly in the model to optimize ease of review. Detailed documentation should also be provided for users interested in evaluating the technical elements of the model.[66]

## Key Outcomes

Cost-effectiveness analyses assess value by relating estimated costs to clinical events, survival, and health-related quality-of-life outcomes. While clinical events (e.g., myocardial infarction, stroke) are interpretable by clinicians, expressing results solely as cost per event avoided limits comparability across diseases. Standardized health outcome measures such as the quality-adjusted life-year (QALY) or equal value life-years gained (evLY) facilitate comparisons of value across conditions and are therefore recommended. Clinical event outcomes, survival, and standardized health outcomes should all be reported. When concerns arise that QALYs may not fully reflect benefits for certain populations (e.g., older adults, people living with disability), supplementary outcome measures may be provided as complementary analyses. These should be viewed as additions rather than substitutes for QALYs.

### Modeling Technique

Common modeling approaches for conducting cost-effectiveness analyses primarily include: (1) decision analysis (i.e. decision trees), (2) Markov (cohort) health state models, and (3) patient-level simulation. The choice of modeling approach may be guided by aspects of the treatment, health condition, or available data, and the modeling strategy should be clearly explained with supporting rationale.

It is recommended that the simplest feasible modeling approach be used. The model should be sophisticated enough to capture the key aspects of the disease and treatments yet be well supported by high-quality data that are available to and interpretable by the user. Models that have been previously developed may be adapted for use in the AMCP dossiers. Evidence supporting the validity of existing models should be provided, as well as sufficient documentation and transparency on their design, functioning, and data inputs. Because cost-effectiveness models are simplified views of disease processes, specifying the model structure is important. Developers of such analyses should employ validated model frameworks, if available, and seek input from clinicians to ensure that models have good face validity for the disease or condition being evaluated.

### Perspective and Time Frame

The HCDM (i.e. payer) perspective is recommended for the primary analysis, while the societal/modified societal perspective can also provide further insight into the broader longer-term values of the product. Additional supplementary perspectives (e.g. employer) may also be provided where relevant. The model should consider a time horizon that is appropriate to the disease being studied and be long enough to reflect all important differences in costs and outcomes between the products being compared. Future costs and health gains should be adjusted for time preference, typically using a discount rate of 3%.[71]

## 4.2.2B Data Sources

The identification, selection, interpretation, and use of data to inform the model are key to the modeling process and should receive ample attention from model developers and users. The analysis should be based on the highest-quality and most up-to-date clinical, epidemiologic, patient, and economic data available from the sources most relevant to the model. The process for identifying, evaluating, and selecting data for the model should be clear and systematic. Well-designed RCTs will generally serve as the most valid source for efficacy and safety inputs, but sensitivity analyses may include data from real-world evidence studies from larger populations in more realistic conditions. Ideally, comparative trials that evaluate treatments directly should be used. In the absence of such studies, indirect comparisons may be used. In general, relevant studies should:

1. Directly or indirectly compare and quantify treatment effects and other relevant patient-reported outcomes (including quality of life).
2. Incorporate individual preferences (i.e. utility) for health gains and adverse effects.
3. Quantify costs and benefits over the natural course of the disease.
4. Assess resources used to support alternative therapies.
5. Evaluate the effect of uncertainty on the results of the analysis.

Data inputs characterizing typical healthcare utilization for the condition of interest should be drawn from U.S. health system sources and adjusted to the model year. Disease trajectories may be informed from clinical or epidemiologic studies. When empirical data are unavailable, modelers may draw from large population databases or structured expert input, and all such sources should be described with sufficient detail to support transparency and interpretation. Parameter estimates used in the model for the product under consideration should be closely linked with the evidence provided in all sections of the Approved Product Dossier. Model assumptions should be clearly explained. In addition to the identification of base-case estimates for the model, ranges for parameters should, whenever possible, be based on observed distributions, and well-referenced.

## Drug Effectiveness

When available, RCT data should be assessed and considered as the basis of all efficacy (i.e. effectiveness) estimates. Justification should be provided for inclusion and exclusion of any RCTs potentially relevant to the analysis. When available, real-world evidence, including prospective and retrospective observational trials, and direct and indirect comparisons should be assessed for relevance and validity, particularly when such evidence further informs outcomes for populations that were underrepresented in RCTs. If appropriate, these data should also be incorporated into the model or addressed in sensitivity analyses. Key uncertainties of the effectiveness measure should be disclosed, particularly when involving the representation of important patient subgroups and generalizability to real-world populations.

## Drug Safety Data

Clinically relevant adverse events observed in RCTs should be included in the model, as well as any significant safety signals derived from other study types (e.g., observational studies and/or real-world evidence). The economic impact of treatment-related adverse events should be incorporated into cost-effectiveness analyses. A wide range of estimates of potential safety outcomes should be explored given the challenge of accurately ascertaining the likelihood of low-probability events.

### Cost Data

Unit cost data ideally would be relevant to HCDMs, based on health care system data. If specific health care system data are not available, costs from representative U.S. private payers, Medicare, and other sources may be used. Because the costs of infused and injected drugs may also depend on the site of care, models should take these attributes into consideration. Real-world evidence may also inform estimates of related medical costs and utilization patterns. Decision-analytic models should be sufficiently reflective of U.S. health system practice and payment patterns. Additionally, the methodology should clearly explain how the model addresses patient cost-sharing for the treatment(s) evaluated and assumptions about patient adherence.[70]

### Utilities

Preference estimates should ideally be derived from studies surveying either patients or the U.S. general population, using a direct elicitation method, such as time trade-off or standard gamble, or an instrument, such as the EuroQol (EQ-5D), Health Utilities Index (HUI), Short Form-Six Dimension (SF-6D), or Quality of Well-Being (QWB). While utilities should ideally be derived from U.S. population preferences, this may be impractical in some situations and utilities derived from trials or from populations of other nations may be used.

### Demographic and Practice Pattern Data

Ideally, the model should reflect typical U.S. demographic and practice pattern data. Variation in treatment patterns (e.g., diagnostic intensity, treatment sequencing, follow up care) may meaningfully influence both costs and outcomes and should therefore be explored in sensitivity analyses.

### Surrogate Markers

When surrogate markers are used to model longer-term outcomes, specific evidence should be provided supporting their validity.

### Expert Opinion

Data derived from expert panels are not acceptable for key effectiveness or safety variables. However, this approach may be reasonable for other variables where estimates are not available through literature, databases, trials, or other typical sources. In such cases, the expert assumptions should be clearly stated and thoroughly tested in sensitivity analyses.

### Efficacy Versus Effectiveness

When feasible and scientifically plausible, efficacy results from RCTs should be transformed into effectiveness parameters. For example, this may involve inclusion of an

adherence parameter into the model based on observational data. Documentation and a clear description of the methodology will be necessary for health care system staff to evaluate the validity of this approach.

### Real-World Evidence

While RCTs provide fundamental efficacy and safety data, real-world evidence can provide valuable supplemental insight (e.g. to inform extrapolation over long time periods). Prospective or retrospective observational data may include larger populations than RCTs and reflect real-world conditions and practical utilization, which may enhance a model's robustness and applicability. Real-world evidence may be more limited in quality due to the observational nature of data, greater risk of confounding in an uncontrolled environment, and limitations of current data sources.

## 4.2.3B Conduct

### Measure of Effect

The expected (average) clinical and economic outcomes should be calculated and presented for each strategy evaluated, along with incremental costs, incremental effectiveness, and incremental cost-effectiveness ratios where appropriate. Differences in absolute risk of clinical events should be reported, health care cost offsets and intervention costs should be presented both separately and in aggregate. Clinical risk-benefit trade-offs should be explicitly presented and discussed. Average cost-effectiveness ratios (e.g., cost per responder) may be provided but should be considered complementary and not a substitute for incremental cost-effectiveness analyses comparing the product with relevant comparators.

### Sensitivity Analysis

Both deterministic (1-way) and probabilistic (multiple-way) sensitivity analyses (PSA) should be conducted to assess the robustness of the results. Tornado diagrams are encouraged to present one-way sensitivity analyses, displaying parameters form greatest to least influence on the results. For PSA, a probability distribution assigned to each parameter should be provided, and the associated distributional assumptions (e.g. parameters or moments) should be disclosed in the methods. Use of generally accepted confidence intervals (95%) should be employed if parameter uncertainty is, at least largely, characterized by random error. Cost-effectiveness scatterplots and acceptability curves are recommended to display the results of the analysis. Scenario analyses testing the structural assumptions of the model are also highly recommended.

## 4.2.4B REPORTING THE RESULTS OF COST-EFFECTIVENESS ANALYSIS

[Note for public comment: Proposed section 4.2.4B is currently section 4.4.2B in Format v5.0. Only proposed updates to wording are highlighted in this section.]

The cost-effectiveness modeling report should follow this format: (1) Introduction/Background, (2) Methods, (3) Results, (4) Discussion and (5) Limitations. A 500-word abstract following this same format should be provided on the first page of the modeling report and include an explicit description of the key drivers of the model results identified in sensitivity and scenario analyses.

Below are the minimum recommended figures and tables for economic models. Multiple tables in each category (e.g., Table 1a, 1b) may be used, if needed, based on the modeling approach being presented.

- **Figure 1**. Provide a figure displaying the structure of the model (e.g., a decision tree, Markov model). A simplified schematic diagram may be used for ease of presentation, but a detailed figure should also be included.
- **Table 1**. Provide a table listing all the model inputs, including probabilities, costs, and utility estimates if appropriate. Provide a range of values on which sensitivity analyses are based for each input.
    1. Include references in the table for all inputs, including ranges.
    2. Note in the table any estimates that lack supporting evidence.
- **Table 2**. Provide an explicit list of model assumptions, including assumptions about comparator interventions, clinical events, patient management, delivery, administration, setting of care, and costs.
- **Table 3**. Present the disaggregated results in a table (e.g., cost-consequence style, with costs presented separately from health outcomes). Data presented in this format are more easily understood and interpreted by health care system formulary committees. The following specific data should be presented for each strategy as appropriate for the analysis type:
    1. The projected clinical events (e.g., heart attacks, cirrhosis, recurrence).
    2. The life expectancy, QALY estimates, and/or other measured outcomes.
    3. Total health care costs over the model time horizon.
    4. The cost of implementing therapy, including all anticipated costs of care management, delivery, administration, and setting of care, and the resulting cost offsets.
    5. Incremental cost-effectiveness ratios.
- **Figure 2**. Present one-way sensitivity analyses on all model inputs in a figure (e.g., tornado diagram) or a table.
    1. Clearly present the model inputs or assumptions that drive the difference in (1)

costs, (2) effects, and (3) incremental cost-effectiveness.
2. When appropriate, present multiway (e.g., two-way, best- and worst-case scenario, probabilistic) sensitivity analyses.

### CHEERS Guidance for Reporting the Results of Economic Analysis

In addition to the general guidance provided above, reporting of economic results should follow the recommendations of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) issued by the ISPOR Task Force on Economic Evaluation guidelines.[74]

#### 4.2.5B Interactive Cost-Effectiveness Models

While CEAs may include interactive or user-modifiable components, these should be understood as tools for transparency and scenario exploration rather than as mechanisms for local plan-level recalculation. When simplified or user-facing versions are provided, manufacturers should clearly note simplifications, fixed assumptions, and the implications for applicability and transferability of results.

## 4.3B Budget Impact Model

### 4.3.1B Approach and Framework

### Guidelines

Budget Impact Analysis (BIA) shares many similar features with CEA (e.g. ascertaining costs, performing sensitivity analysis), and relevant guidance for CEA above also applies to conducting BIAs, particularly regarding clarity and transparency in reporting. The modeling approach and analytic framework of the budget impact model should generally follow the recommendations below and guidance provided by ISPOR.[75]

The budget impact model should be based on a health care system perspective and take the following into consideration:

1. Characteristics of a health system, such as prevalence and incidence of disease among the population, aspects of the benefit design, and other factors that may affect access.
2. Use and cost of current mix of therapies used to treat the condition.
3. Projected use and costs of the new mix of therapies to treat the condition.
4. Costs and cost offsets associated with changes in use of health services due to the new product.

### Perspective and Time Frame

The perspective of the HCDM organization is recommended. The time horizon of the model should be of relevance to the HCDM, typically one to three years in alignment with common payer decision horizons. Where relevant, models should capture broader short-term health care impacts associated with the use of the new product (e.g. reduced treatment for acute side effects of alternative therapies). Dynamic models are recommended for BIAs that use a multiple year timeframe, particularly when a product alters future disease epidemiology.

### Population

The target population for a budget impact model should include all patients eligible to receive the new intervention during each year of the modeled time horizon. The modeled population should reflect dynamic entry and exit of eligible patients each year rather than following a static cohort over time.

### Treatments

Projections about the uptake of the new product should be explained, including the potential role of utilization management strategies and other factors that may affect access. Rationale for treatment uptake rates should be provided. The cost of therapy captured in the model should reflect the cost borne by the health system (not including patient cost-sharing). Assumptions regarding the projected level of patient adherence should be explained.

## 4.3.2B Data Sources

The base-case model (as presented in the written dossier) should be representative of a general commercial, Medicare, or Medicaid plan population. However, the model should be sufficiently flexible to allow users to input data specific to their setting, such as size of the population, prevalence of the condition, and estimated and projected costs and cost offsets.

## 4.3.3B Conduct

### Results

When reporting the budget impact of the treatment, it is recommended to present the findings as both the PMPM cost difference and the overall budget impact on the health system. Cost per-treated-member-per-month (PTMPM) may also be reported but should not substitute for PMPM because it does not reflect costs spread across the full enrollee population. Although no absolute affordability threshold exists for changes in PMPM, manufacturers are encouraged to interpret results by describing the budgetary implications and noting when projected changes may represent substantial cost exposure for payers.

### Sensitivity Analysis

Sensitivity analyses are essential for assessing parameter uncertainty within the budget impact model and should also assess structural uncertainty in model design and assumptions. Any expected off-label use of the new health technology should not be included in the main budget impact analysis but may be considered in scenario analyses.

## 4.3.4B Interactive Budget Impact Models

When possible, a stand-alone, electronic, transparent and customizable interactive model should be provided to HCDMs. Interactive BIA models are intended to support operational forecasting and plan-level affordability assessment. To meet these needs, BIA models should:

1. Be provided in a modifiable electronic format (e.g., Excel or equivalent) with unlocked input fields and clear structure for user-defined analyses. Cloud-based or alternative platforms are acceptable if they allow equivalent transparency, modifiability, and data export.
2. Allow the user to substitute plan-specific values for key drivers including population size, epidemiology, market share/uptake, utilization patterns, unit costs, and negotiated prices or rebates.
3. Clearly differentiate default values from modifiable values and provide sources or rationale for all default inputs.
4. Provide automated analyses relevant to payer evaluation, including gross and net budget impact, one-way sensitivity analysis, and scenario analysis for alternative uptake or contracting strategies.
5. Include a brief data dictionary and model guide describing sheet purpose, model structure, and calculation flow sufficient for an analyst to follow the logic.
6. Incorporate guardrails to prevent implausible input values.
7. Support relevant subpopulation analysis when the indication, coverage policy, or real-world use implies segmentation (e.g., age bands, comorbidity groups, benefit design variation).

### Model Provision and Accessibility

Manufacturers should make interactive BIAs available to HCDMs electronically following discussion of model design, assumptions, and results. If an interactive model is not available, this should be clearly stated in the modeling report along with the manufacturer's standing policy for model access. Publication in peer-reviewed literature and periodic updating with real-world evidence are encouraged.

### User Responsibilities

Model users should recognize that local data availability varies and that modifying inputs outside reasonable bounds may yield non-credible estimates. Users should apply modifications consistent with available evidence and organizational assumptions.

## About AMCP

AMCP is the professional association leading the way to help patients get the medications they need at a cost they can afford. AMCP's diverse membership of pharmacists, physicians, nurses, biopharmaceutical professionals, and other stakeholders leverage their specialized expertise in clinical evidence and economics to optimize medication benefit design and population health management and help patients access cost-effective and safe medications and other drug therapies. AMCP members improve the lives of nearly 300 million Americans served by private and public health plans, pharmacy benefit management firms, and emerging care models.

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