



Format 4.1 Revision

Format for Formulary Submissions

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

Select Provisions for Public Comment

INTRODUCTION & CONTENTS

A revision is being proposed to the *AMCP Format for Formulary Submissions*, version 4.1, to specifically update the following key areas: digital therapeutics, health disparities, guidance on PIE decks, and to encourage brevity in the document. The following are select provisions for public comment.

AMCP Format for Formulary Submissions

Public Comment Period Questions • June 2023

Digital Therapeutics

1. Does this section properly convey information incorporating digital therapeutics into the *AMCP Format*? **2**
2. Does the following table encompass all the important/unique product information considerations for formulary evaluation of digital therapeutics? Is the layout conducive to efficient review? **6**

Health Disparities

3. What is the feasibility of manufacturers to provide this information? What is the demand for this information among payers? **9**
4. The intent is that the dossier explains if/how patient cost sharing was captured in the pharmacoeconomic model. Does this come across in the new language? **12**
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Format of the *Format*

6. The goal was to balance brevity without sacrificing clarity, does this meet the objective? **19**
7. From an efficiency standpoint, we are proposing to use external hyperlinks for product information, websites, and guidelines. How would this affect your resources? **27**
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PIE Deck Guidance

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DIGITAL THERAPEUTICS

QUESTION 1: DIGITAL THERAPEUTICS

- Does this section properly convey information incorporating digital therapeutics into the *AMCP Format*?

SECTIONS WITH PROPOSED REVISIONS:

- Special Content Considerations (addition of Digital Therapeutics section)

**Proposed revisions are highlighted in yellow.*

SPECIAL CONTENT CONSIDERATIONS

Digital Therapeutics

The Academy of Managed Care Pharmacy defines digital therapeutics (DTx) as products designed to stand alone or work in combination with existing medications or treatments, helping patients prevent, treat, and/or manage their disease while ensuring optimal health outcomes from therapy. A key distinguishing feature of a prescription (or regulated) DTx product is that it makes a health claim that is validated by a third party (e.g., a regulatory authority).¹ However, definitions of digital health, digital therapeutics, and digital health technology differ across various sources and are generally broad, encompassing many types of products.^{2,3} Digital therapeutics may be standalone products or used in conjunction with a specific drug or class of drugs. The *AMCP Format* is intended to be used with prescription digital therapeutics though manufacturers of digital health products may develop dossiers, if warranted.

¹ AMCP. AMCP Partnership Forum: Digital Therapeutics—What are they and where do they fit in pharmacy and medical benefits. *J Manag Care Spec Pharm*, 2020 May;26(5):674-681. Available at: <https://doi.org/10.18553/jmcp.2020.19418>. Accessed May 17, 2023.

² National Institute for Health and Care Excellence. Evidence standards framework (ESF) for digital health technologies. Available at: <https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies>. Accessed May 17, 2023.

³ Digital Therapeutics Alliance. DTx Value Assessment & Integration Guide. Available at: https://dtxalliance.org/wp-content/uploads/2022/05/DTx-Value-Assessment-Guide_May-2022.pdf. Accessed May 17, 2023.

Definitions Related to DTx (Adapted from AMCP Partnership Forum Proceedings: The evolving role of digital therapeutics)⁴

Term	Organization	Definition	Categories
Digital Therapeutics	AMCP	Products designed to stand alone or work in combination with existing medications or treatments, helping patients prevent, treat, and/or manage their disease while ensuring optimal health outcomes from therapy. A key distinguishing feature of a prescription (or regulated) DTx product is that it makes a health claim that is validated by a third party (e.g., a regulatory authority).	<ul style="list-style-type: none"> • Treat a disease • Manage a disease • Improve a health function (e.g., prevent a disease)
	Digital Therapeutics Alliance	Deliver evidence-based therapeutic interventions that are driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.	
Digital Health	US Food and Drug Administration	Technologies that use computing platforms, connectivity, software, and sensors for health care and related uses.	<ul style="list-style-type: none"> • Mobile health • Health information technology • Wearable devices • Telehealth/ telemedicine • Personalized medicine
Digital Health Technologies	National Institute for Health and Care Excellence	Apps, programs, and software used in the health and social care system. They may be stand-alone or combined with other products such as medical devices or diagnostic tests.	<ul style="list-style-type: none"> • Provide an intervention • Aid understanding/ communicating • Offer system services

⁴ AMCP. AMCP Partnership Forum: The evolving role of digital therapeutics. *J Manag Care Spec Pharm*, 2022 Jul;28(7):804-810. Available at: <https://doi.org/10.18553/jmcp.2022.22093>. Accessed May 17, 2023.

The role of the AMCP *Format* in assessing digital therapeutics is the same as with prescription pharmaceuticals—to convey evidentiary needs. The goal of the dossier is to standardize communication of the evidence and supplemental information for evaluation of multiple types of products based on their benefit/risk profile, alternative options, and place in therapy. Given the breadth of volume of DTx products coming to the market, standardized resources will be critical in allowing decision makers to systematically evaluate DTx for coverage or to incorporate them into a treatment regimen.

Because of the vast number, type, and complexity of products, and evolving nature of the class, additional information may be needed on the following:

- Functionality
- How the DTx is made available (app, computer program, website)
- Compatibility (i.e., software and/or hardware necessary to utilize product)
- Instructions for use and intended care setting
- Place in therapy (is the product intended to be used with certain drugs or classes of drug—or could it be used as a standalone product)
- Available versions (i.e., different languages or formats)
- Technology assistance/support available
- Real world evidence
- Regulatory codes, classifications, and identifiers
- Billing and reimbursement codes

These items may be addressed in the dossier through existing sections. Place in therapy, functionality, and compatibility may be addressed in section 2.0B Production Information and Disease Description, and any trials and/or real-world evidence may be placed into their appropriate sections within Section 3.0 Clinical Evidence. Other types of evidence and studies that do not fit within Section 3.0, such as preference testing, usability testing, and information on the validation of the endpoints/scales, may be included in section 5.0 Additional Supporting Evidence. The dossier must clearly specify which version of the DTx product it addresses.

Additionally, a **“Table of Highlights for Digital Therapeutics”** may be included in the product information section of the dossier.

Given the potential complexity of regulatory processes, data sources, and manufacturer relationships, the AMCP *Format* includes the following approaches for developing dossiers:

- DTx as a Stand-alone Therapy: If the digital therapeutic is a software only intervention independent of other pharmaceutical products or the digital therapeutic is intended to be as add-on therapy to other standard of care treatments, a stand-alone dossier should be developed.
- DTx Utilized with Other Therapies: If the digital therapeutic is intended to be used with certain classes of medications (i.e., insulin or inhaled medications for asthma), a stand-alone dossier should be developed.

- The digital therapeutic is co-developed or intended to be used with a specific pharmaceutical product:
 - > If the DTx is required in the drug label, the manufacturer should, if possible, provide data on the clinical utility and economic value of both the pharmaceutical and DTx in a single dossier.
 - > If the DTx is not required in the pharmaceutical label, then the developer may develop a separate dossier that provides information as outlined in the AMCP *Format*.

Optional Appendices:

Privacy and data security: Information related to privacy and security is not required to be included in an AMCP dossier as the intended audience is healthcare decision makers who may lack the expertise needed to thoroughly evaluate the privacy and data security specifications for DTx products. Manufacturers may create additional appendix sections if they determine that privacy and data security elements are needed in their dossier. If needed, payers may seek additional expertise from data IT/security experts, establish a DTx subcommittee, or have a separate group, such as an innovation center, assist with DTx evaluation. Digital therapeutics manufacturers may work directly with payers and health systems to integrate and implement digital therapeutics.

Engagement: Manufacturers may specify how they define engagement in an optional appendix. Due to the wide variety of digital therapeutics, available measures for engagement, user satisfaction, and active users have not been standardized. Furthermore, standard measures used for traditional products, such as adherence and persistence may not apply to digital therapeutic products. If engagement measures were used in clinical trials or real-world evidence, they may be addressed in Section 3.0 or Section 5.0.

Screenshots: Screenshots of the patient-facing or clinician facing application may be included in the dossier as an optional appendix. If included, the version number of the application must be stated. Links to external websites intended for healthcare professionals may also be included.

DIGITAL THERAPEUTICS

QUESTION 2: DIGITAL THERAPEUTICS

- Does the following table encompass all the important/unique product information considerations for formulary evaluation of digital therapeutics? Is the layout conducive to efficient review?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Unapproved Product Dossiers, Sections 2.0, 2.1A
- Evidence Recommendations for Approved Products Dossiers, 2.0, 2.1B, 2.1.2B
- Evidence Recommendations for Unapproved Use Dossiers, Sections 1.0C, 1.2C

**Proposed revisions are highlighted in yellow. Please note that all revisions for the Evidence Recommendations for Approved Product Dossiers sections 2.0B, 2.1.1B, and 2.1.2B are included below for completeness but only 2.1.2B reflects the DTx revisions. When answering Question 2, please refer to 2.1.2B.*

EVIDENCE RECOMMENDATIONS FOR APPROVED PRODUCT DOSSIERS

2.0 B PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1.1 B PRODUCT DESCRIPTION

The recommended length of Section 2.1B is five pages (maximum 10).

This section can be written in paragraph or as a **table (preferred)**. Brevity should be considered when writing this section. When possible, use language from the highlights section of the USPI or hyperlink to the USPI.

Basic product information should generally be provided, including but not limited to:

- Generic name
- Brand name
- FDA-approved indication(s) and approval date
- Therapeutic class
- Dosage forms and strengths
- Contraindications
- Boxed Warning
- Warnings/Precautions
- Adverse events
- Unique Device Identifiers (e.g. NDC number, AHFS)
- Wholesale acquisition cost (WAC) pricing

Other differentiating attributes may also be included, when clinically necessary.

- Pharmacology (MOA/pharmacokinetics/pharmacodynamics).
- Special populations (e.g., pregnancy, pediatric use, renal impairment).
- Drug/drug, drug/food, and drug disease interactions.
- Access (e.g., restrictions on distribution, supply limitations, anticipated shortages, patient assistance, and prescribing restrictions).
- Product development or post-marketing obligations as required by the FDA.
- Post-approval monitoring of drug safety and adverse events.
- Co-prescribed/concomitant therapies.

Additional information beyond the label should only be provided in cases where one or more of these attributes is of major significance in defining the value of a product.

2.1.2 B PRODUCT DESCRIPTION—DIGITAL THERAPEUTICS

For a digital therapeutic product, please include applicable components of Section 2.1.1B and the following.

Table for Digital Therapeutics

<i>Type of Information</i>	<i>Description of Information</i>
Product name	Name of digital therapeutic product
Product version	Include version of application that the dossier applies to
Approval pathway	FDA clearance, class II device, predicates based on the desktop app now transferred to the web, etc.
Intended environment of therapy delivery and ongoing use	<ul style="list-style-type: none"> • Patient setting (home, work, school) • Healthcare setting • Institutional setting (nursing home, long-term care)
Intended line of business	<ul style="list-style-type: none"> • Commercial, Medicare, Medicaid
Relationship to other therapies	<ul style="list-style-type: none"> • Standalone • Add-on therapy to standard of care • Replaces existing therapy • Co-prescribed with pharmacologic therapy
Language	<ul style="list-style-type: none"> • Languages the product is available in
Considerations for specific populations	<ul style="list-style-type: none"> • Additional information on cultural, disability, age, health or digital literacy requirements

Type of Information	Description of Information
Patient access to the product	<ul style="list-style-type: none"> • Formal prescription from a qualified clinician (in-person or virtual engagement) • Clinician referral for a non-prescription DTx product (in-person or virtual engagement) • Direct authorization by an employer for a non-prescription DTx product • Direct authorization by a payor for a non-prescription DTx product • “Authorized clinical protocol” established by a HCDM to authorize automatic patient access, when necessary, qualification requirements are met • “Clinically validated screening tool” that patients use to determine whether they qualify for the therapy » “Over-the-counter” model where no form of third-party authorization is necessary • Details on the dispensing process may also be included (e.g., download, specialty pharmacy, etc.)
Components required for the software to deliver its therapeutic value	Additional hardware or software required
Host technology and required hardware components (if applicable)	Smartphone, tablet, laptop, wearable device
Technical requirements	<ul style="list-style-type: none"> • Offline-capable • Broadband
Compatibility	<ul style="list-style-type: none"> • PC/MAC • Browser (Chrome, Edge, Safari) • iOS • Android
Technical assistance availability	Is there in-app support via chat or call center availability.

HEALTH DISPARITIES

QUESTION 3: HEALTH DISPARITIES

- What is the feasibility of manufacturers to provide this information?
- What is the demand for this information among payers?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Approved Product Dossiers, Section 3.0B

**Please note that all revisions for the Evidence Recommendations for Approved Product Dossiers section 3.0B are included in yellow below for completeness but only the words in blue font reflect the health disparities revisions. When answering Question 3, please refer only to the text in blue font.*

EVIDENCE RECOMMENDATIONS FOR APPROVED PRODUCT DOSSIERS

3.0B CLINICAL EVIDENCE

Section 3.0B should consist of clinical studies that support the use and value of the product in a clear and concise format.

It is important that Section 3.0 is transparent and reflects the full body of clinical evidence that exists for a product. For a new product, available evidence may be limited to a few studies, and inclusion of all studies in the dossier is sensible. For a product that has been available for several years, there may be a very large number of studies in the medical literature and inclusion of every study may be impractical for both manufacturers and HCDMs. In such cases, it is important that the manufacturer exhibit transparency and fair representation concerning the evidence included in the dossier, while at the same time providing a dossier that is useful and manageable for HCDMs. Therefore, it is recommended that in such cases, the evidence be separated into the following categories:

1. **An overview of information contained in Chapter 3.0** should be provided on page 1.
2. Pivotal data, and in some instances other RCTs and/or RWE, that contribute significantly to the knowledge base of the product should be included as **study summaries and evidence tables**.
3. Informative but smaller and/or less rigorous studies that may add to the evidence base should be included as **evidence tables only**.
4. All other studies that have been reported but do not add significantly to the knowledge base of the product should be identified in a **bibliography only**.

The overview of the information contained in Chapter 3.0 should define a specific set of objective criteria for inclusion and exclusion of studies and describe how studies were selected for inclusion and exclusion in this section. Studies excluded do not need to be identified in a bibliography. Considerations for establishing inclusion or exclusion criteria can be based on the study characteristics as is done in clinicaltrials.gov. These characteristics include but are not limited to, study design, number of subjects, and location of the study. In this section, the manufacturer should clearly explain the objective rationale for delineation and assignment of studies into each of the categories above to avoid selection bias. As these definitions may vary depending on the context of the product, clinical setting, and available treatment alternatives (e.g., common disorder vs. orphan disease), the manufacturer should justify how studies are included (study summaries vs. evidence tables vs. bibliography).

This section should also explain the degree to which study subjects represent the target population as described in 2.2.1 B Disease Description, and identify differences that may obscure translation to real-world effectiveness. [For clinical trials, the diversity of study participants should be explained and supplemental tables depicting trial representativeness are strongly encouraged. Retrospective studies should include subgroups disproportionately affected by the health condition, and data limitations that erode generalizability should be disclosed.](#)

Considerations for Chapter 3.0:

- The length and level of detail for study summaries and evidence tables may vary based on the amount of available data. It must be noted that HCDMs want concise, focused, and user-friendly presentation of data. One of the most common complaints from HCDMs is that dossiers are too long.
- Specific study designs are not prescribed in this section. Manufacturers should include studies that generate evidence about clinical outcomes.
 - > Prospective clinical studies including RCTs, observational data, registries, real-world evidence, and other studies that measure clinical endpoints should generally be included in Chapter 3.0. Study results and outcomes may include efficacy, safety, tolerability, pharmacokinetics/ pharmacodynamics, patient preference, patient adherence, patient-reported outcomes, quality of life, evidence that identifies patient subgroups or clinical settings in which the product may be appropriate, and other clinically related outcomes.
 - > Retrospective studies, including real-world evidence, supporting the clinical use and clinical value of the product that are conducted using existing data from chart reviews, medical and pharmacy claims, electronic medical records, product and/or disease registries, patient-generated data including data gathered from other sources such as mobile applications, or other novel sources of data.
 - > In vitro, animal, and phase 1 studies are generally not included unless the value proposition is based on relevant pharmacologic, pharmacodynamics, or pharmacokinetic evidence in these earlier studies.

- Studies available from published medical journals are preferred. When publications are not available, medical congress abstracts, posters, and scientific podium presentations can be considered. Publicly available information from manuscripts submitted or accepted by medical journals, Clinicaltrials.gov, FDA briefing documents and manufacturers' data on file can also be used, when applicable.
- Comparative evidence is a necessary component of a comprehensive product dossier. For this reason, it is strongly recommended that head-to-head clinical studies between the product and its primary comparators be included in Chapter 3.0. In the absence of head-to-head data, other comparative efficacy and safety analyses may be considered.
- If the results of a trial have been reported in more than one journal article or conference abstract, poster, or oral presentation, all may be combined into one summary and one row of an evidence table, citing all the sources from which data have been drawn and clearly stating the total number of subjects. Discuss important study findings and comment on their implications for different patient populations.
- Potential off-label uses are of significant interest to HCDMs. As such, clinical studies involving off-label uses should be included in dossiers. Manufacturers should clearly delineate evidence for on- and off-label uses (i.e., organize and report on-label indications and information first and off-label after). If data regarding off-label use have been submitted to the FDA for approval but the FDA decision was to deny the approval of the proposed new indication, then the FDA decision should be briefly summarized.
- For products with more than one approved indication, the pharmaceutical manufacturer should decide how studies for labeled indications should be presented. If the manufacturer decides to have separate dossiers for each approved indication, those requesting dossiers must be apprised of the existence of more than one dossier, and that each can only be supplied pursuant to an unsolicited request. In all cases, however, all studies for a given indication should be grouped together in the dossier.
- For pharmaceuticals designated by the FDA as "breakthrough drugs," evidentiary reporting requirements are the same as for other drugs. For biosimilars, basic evidentiary needs are the same as for "traditional" and "specialty" pharmaceuticals. While it is recognized that trials dealing with interchangeability, dosing equivalency, comparison with innovator agents, etc. are especially important, all trials dealing with biosimilars should be reported since there is often limited data available for such products, and HCDMs need access to all relevant evidence and data.
- Data summarized in Chapter 3.0 should not be also summarized in 5.0.

HEALTH DISPARITIES

QUESTION 4: HEALTH DISPARITIES

- The intent is that the dossier explains if/how patient cost sharing was captured in the pharmacoeconomic model. Does this come across in the new language?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Approved Product Dossiers, Section 4.2B, 4.2.2B

**Please note that all revisions for the Evidence Recommendations for Approved Product Dossiers sections 4.2B and 4.2.2B are included in yellow below for completeness but only the words in blue font reflect the health disparities revisions. When answering Question 4, please refer only to the text in blue font.*

EVIDENCE RECOMMENDATIONS FOR APPROVED PRODUCT DOSSIERS

4.2 B COST-EFFECTIVENESS ANALYSIS

4.2.1 B APPROACH AND FRAMEWORK

Guidelines

In general, the cost-effectiveness framework should consider recommendations published by ISPOR and SMDM Modeling Good Research Practices Task Force.

The model should be disease-based and depict the following:

1. Disease or condition, patient population, natural history, clinical course, and outcomes.
2. Relevant treatment options and the treatment process for each option—preferably based on treatment guidelines or actual practice.
3. Costs of the product and other medical resources consumed within each clinical pathway.
4. Economic impact of adverse events and costs of monitoring for both therapeutic effect and adverse events.
5. Outcomes of therapy for each clinical pathway.
6. Incremental cost and outcomes analysis presented in cost/consequences tables and as cost-effectiveness ratios.

Analytic Framework

The general category of cost-effectiveness models includes analyses that value outcomes by assessing clinical events, life expectancy, and QALYs. Clinical events are more readily interpretable by clinicians and allow for direct assessment of the effect of clinical data but cost-per-event-avoided calculations are not comparable across disease areas. In contrast, QALYs allow for assessment of overall health care value, but may be more difficult to interpret from a health care system perspective. It is thus recommended that clinical events, life expectancy, and QALYs all be assessed, with the latter two outcomes primarily relevant for lifetime time frame analyses. Clinical events can serve as a supplemental analysis. The results should be reported separately, as outlined subsequently in this section. Exclusion of any of these endpoints should be justified. If possible, use of surrogate endpoints should be avoided since they are not as useful as final endpoints in decision-making.

Modeling Technique

There are several decision-analytic based approaches to constructing disease-based cost-effectiveness models, primarily: 1) decision trees, 2) Markov (cohort) models, and 3) patient-level simulation (discrete event simulation). There are advantages and disadvantages to each technique, mainly related to the conflicting factors of transparency and data availability versus the complexity of many diseases and their treatments.

It is recommended that the simplest feasible modeling approach be used. In other words, 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.

Perspective and Time Frame

The HCDM perspective is recommended for the primary analysis, with optional perspectives (e.g., societal, employer) conducted as secondary evaluations. The model should consider a time horizon that is appropriate to the disease being studied and reflect the decision-making and financial and budget constraints consistent with the perspective. The time horizon should be long enough to reflect all important differences in costs and outcomes between the technologies being compared. Adjustment for time preference should be incorporated as appropriate and follow U.S. Public Health Service Panel recommendations (discounting both future costs and health effects).

4.2.2 B 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 all the data in the model should be clear and systematic.

It is important that modeled claims for cost-effectiveness derive from well-conducted trials for the treatments of interest. Ideally, comparative trials that evaluate treatments directly should be used. In the absence of such studies, indirect comparisons should be considered. 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. Assess patient and community preferences for alternative therapies.
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 claims made for alternative therapies.

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. All necessary assumptions should be clearly stated. In addition to the identification of base-case estimates for the model, ranges for parameters should be determined and well-referenced.

Drug Effectiveness

When available, RCT data should be assessed and considered as the basis of all efficacy or 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.

Drug Safety Data

Clinically relevant adverse events observed in RCTs should be included in the model, as well as 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 should be explored given the challenge of accurately ascertaining the likelihood of low-probability events.

Economic Data

Unit costs data ideally would be relevant to the decision-maker, based on health care system data. If specific health care system data are not available, costs from representative U.S. private payers, Medicare, and others 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 flexible to adapt the input assumptions to conform to local practice and billing patterns.

Additionally, the model's methodology should consider costs that are borne by payers, the health system and by patients, as relevant to the perspective, where available.

Utilities

Preference estimates should be derived from studies surveying either patients or the general population, using a direct elicitation method or an instrument such as the time tradeoff, standard gamble, EuroQol (EQ-5D), Health Utilities Index (HUI), Short Form-Six Dimension (SF-6D), or Quality of Well-Being (QWB).

Because cost-effectiveness analysis is conducted at the population level, the ideal source of utility values is the general population. This may be impractical in some situations and trial-derived utilities may be used.

Demographic and Practice Pattern Data

Ideally, the model would be interactive, allowing HCDMs to incorporate demographic and practice pattern data, improving the relevance of the model.

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 generally acceptable, especially 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. Inputs obtained from an expert panel should be modifiable in case local opinion leaders disagree with the panel members.

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 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 the fundamental core of efficacy and safety data, real-world evidence may provide valuable supplemental insight. Prospective or retrospective observational data may include larger populations than RCTs and more accurately reflect real-world conditions and practical utilization, which may enhance the robustness and transparency of modeling. 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.

HEALTH DISPARITIES

QUESTION 5: HEALTH DISPARITIES

- What is the manufacturers' ability to address these concerns, particularly at launch? To what extent do payers and manufacturers consider these aspects to be in scope for a new product assessment?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Approved Product Dossiers, Section 5.0B, 5.5B

**Please note that all revisions for the Evidence Recommendations for Approved Product Dossiers section 5.0B and 5.5B are included in yellow below for completeness but only the words in blue font reflect the health disparities revisions. When answering Question 5, please refer only to the text in blue font.*

EVIDENCE RECOMMENDATIONS FOR APPROVED PRODUCT DOSSIERS

5.0 B ADDITIONAL SUPPORTING EVIDENCE

The recommended length of Section 5.0B is two pages (maximum five) for each study or source.

Section 5.0B should consist of all other types of evidence and studies that do not fit in Section 3.0B that support the use and value of the product reported in a clear and concise format. Examples include clinical practice guidelines, HTAs and systematic reviews, compendia, modeling, and pharmacoeconomic and **pharmacoequity** studies.

Similar to Section 3.0B, evidence reported in this section includes the following relevancy criteria: FDA-approved indications and unapproved uses; published and unpublished studies and data; any study regardless of study design; study results regardless of positive, negative, or null findings; and studies inside and outside of the United States.

5.1 B CLINICAL PRACTICE GUIDELINES

Identify important clinical practice guidelines that have been developed and published by medical societies, government agencies, and other national or international organizations that are relevant to the product.

This may also include position statements, consensus statements, clinical pathways, and other similarly termed guidance that are evidence-based and provide specific clinical recommendations. Focus on guideline recommendations specific to the product, its comparators, and the disease state and how the new product is anticipated to be included in or influenced by the guidelines. Summarize information

from clinical practice guidelines briefly and, if feasible, provide a copy of the full guidelines on request or provide links to the original guidelines. The manufacturer should describe how it included or excluded clinical practice guidelines in this section.

5.2 B HTAs AND SYSTEMATIC REVIEWS

Summarize relevant HTAs, systematic reviews, and evidence frameworks (also known as value frameworks) that are available. Examples include Cochrane Collaboration systematic reviews, formal systematic reviews published in peer-reviewed journals, evidence reviews by the Agency for Healthcare Research and Quality (AHRQ), the Patient-Centered Outcomes Research Institute (PCORI), reports from the Institute for Clinical and Economic Review (ICER), and HTAs from recognized public or private organizations, including international bodies such as National Institute of Clinical Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH). Summarize the information that is relevant to the product.

5.3 B COMPENDIA

Summarize important information found in compendia that are officially recognized by the Secretary of Health and Human Services that list the product. Since many compendia publications are available only by subscription and are protected by copyrights, companies may not be able to provide PDF documents or reprints of the relevant content, even if requested by HCDMs. Each manufacturer may determine its own process for handling requests for reprints or copies of compendia information.

5.4 B OTHER ECONOMIC OR OUTCOMES EVIDENCE

Include published studies that result in economic evidence or other outcomes that do not fit in Section 3.0B, for example, pharmacoeconomic, modeling, health care utilization, **pharmaco-equity**, and productivity studies, include real-world evidence. Conduct and reporting of studies in this section should follow accepted practice as evidenced by published methodology and reporting guidelines from reputable professional societies or government agencies. A description of how studies were selected for inclusion should be summarized and included.

Refer to Section 3.0B for items to be included in study summaries and evidence tables. In addition, summaries of economic studies should include the following:

1. Definition of economic endpoints (e.g., mean overall costs, cancer-related cost, \$ per life-years gained, \$ per QALY) including references for standard-of-care costs.
2. Data sources for economic endpoints.
3. Statistical methods/math used to calculate endpoints.
4. Modeling methodology (if applicable).
5. Sensitivity analysis (if applicable).

Refer to Section 3.0B for additional guidance that is relevant for this section (e.g., provide reprints on request, explain criteria for inclusion and exclusion of studies).

5.5 B EFFECT ON QUALITY AND EQUITY

This section is to accommodate information and research where the product has a potential for or demonstrated effect on quality measures that may not fit into any other sections as described by the AMCP *Format*. If no information exists, note that this section is not applicable.

Additionally, phase III RCTs and cost effectiveness analyses typically do not address barriers to the equitable use of a new intervention. Such barriers may include geographic variation in access to specialists, health disparities, and the patient's ability to utilize and afford a medication under current benefit designs. Equity considerations often have implications for the value assessment of a new intervention and should be discussed.

5.6 B OTHER EVIDENCE OR INFORMATION

This section is to accommodate other important and relevant evidence or information that may not fit into any other sections as described by the AMCP *Format*. Examples may include, but are not limited to, in vitro analytical tests or animal studies that demonstrate pharmacokinetics for biosimilar products; other ancillary evidence that demonstrates the uniqueness, benefits, or value of the product; or information regarding effects on patients' family and caregivers. If no information exists, note that this section is not applicable.

FORMAT OF THE *FORMAT*

QUESTION 6: FORMAT OF THE *FORMAT*

- The goal was to balance brevity without sacrificing clarity. Does this meet the objective?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Approved Product Dossiers, Sections 2.1B, 2.2B and 3.0B

**Proposed revisions are highlighted in yellow.*

2.0 B PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1.1 B PRODUCT DESCRIPTION

The recommended length of Section 2.1B is five pages (maximum 10). This section can be written in paragraph or as a **table (preferred)**. Brevity should be considered when writing this section. When possible, use language from the highlights section of the USPI or hyperlink to the USPI.

Basic product information should generally be provided, including but not limited to:

- Generic name
- Brand name
- FDA-approved indication(s) and approval date
- Therapeutic class
- Dosage forms and strengths
- Contraindications
- Boxed Warning
- Warnings/Precautions
- Adverse events
- Unique Device Identifiers (e.g. NDC number, AHFS)
- Wholesale acquisition cost (WAC) pricing

Other differentiating attributes may also be included, when clinically necessary.

- Pharmacology (MOA/pharmacokinetics/pharmacodynamics).
- Special populations (e.g., pregnancy, pediatric use, renal impairment).
- Drug/drug, drug/food, and drug disease interactions.
- Access (e.g., restrictions on distribution, supply limitations, anticipated shortages, patient assistance, and prescribing restrictions).
- Product development or post-marketing obligations as required by the FDA .
- Post-approval monitoring of drug safety and adverse events.
- Co-prescribed/concomitant therapies.

Additional information beyond the label should only be provided in cases where one or more of these attributes is of major significance in defining the value of a product.

2.1.1 B PRODUCT DESCRIPTION—DIGITAL THERAPEUTICS

For a digital therapeutic product, please include applicable components of Section 2.1.1B and the following.

Table for Digital Therapeutics

Type of Information	Description of Information
Product name	Name of digital therapeutic product
Product version	Include version of application that the dossier applies to
Approval pathway	FDA clearance, class II device, predicates based on the desktop app now transferred to the web, etc.
Intended environment of therapy delivery and ongoing use	<ul style="list-style-type: none"> • Patient setting (home, work, school) • Healthcare setting • Institutional setting (nursing home, long-term care)
Intended line of business	<ul style="list-style-type: none"> • Commercial, Medicare, Medicaid
Relationship to other therapies	<ul style="list-style-type: none"> • Standalone • Add-on therapy to standard of care • Replaces existing therapy • Co-prescribed with pharmacologic therapy
Language	<ul style="list-style-type: none"> • Languages the product is available in
Considerations for specific populations	<ul style="list-style-type: none"> • Additional information on cultural, disability, age, health or digital literacy requirements

Type of Information	Description of Information
Patient access to the product	<ul style="list-style-type: none"> • Formal prescription from a qualified clinician (in-person or virtual engagement) • Clinician referral for a non-prescription DTx product (in-person or virtual engagement) • Direct authorization by an employer for a non-prescription DTx product • Direct authorization by a payor for a non-prescription DTx product • “Authorized clinical protocol” established by a HCDM to authorize automatic patient access when necessary, qualification requirements are met • “Clinically validated screening tool” that patients use to determine whether they qualify for the therapy » “Over-the-counter” model where no form of third-party authorization is necessary • Details on the dispensing process may also be included (e.g., download, specialty pharmacy, etc.)
Components required for the software to deliver its therapeutic value	Additional hardware or software required
Host technology and required hardware components (if applicable)	Smartphone, tablet, laptop, wearable device
Technical requirements	<ul style="list-style-type: none"> • Offline-capable • Broadband
Compatibility	<ul style="list-style-type: none"> • PC/MAC • Browser (Chrome, Edge, Safari) • iOS • Android
Technical assistance availability	Is there in-app support via chat or call center availability.

2.1.1 B PRODUCT COMPARISON

A statement as to why the comparators were selected should be included (e.g., meta-analyses, guidelines, literature search). If comparator products are selected based on guidelines, it may be necessary to include information from the guidelines in the product comparison table.

Concise comparison of PI information with the primary comparator products in the same therapeutic area, generally including, but not limited to indications, contraindications, dosing, boxed warning, warning/precaution, AEs, and other differentiating characteristics (expand as appropriate for the therapeutic

class). This information should generally come from the highlights section of the USPI. If direct head-to-head trials have been conducted comparing the product to its comparators, this should be noted here, and the reader referred to the review of those trials in Section 3.0B of the dossier.

For biosimilar products, comparator information about the reference product should be included as well as evidence that demonstrates biosimilarity or interchangeability.

2.2 B PLACE OF THE PRODUCT IN THERAPY

The recommended length of Section 2.2B is 5 pages (maximum 10) for each indication.

Information presented in this section should be brief. Do not duplicate information presented in Sections 3.0B, 4.0B, and 5.0B. Hyperlinks within the document can be useful to encourage brevity when possible.

2.2.1 B DISEASE DESCRIPTION

The disease description should be a **top-line overview** focusing on the specific patient populations for which the product is indicated or seeking an indication.

Manufacturers should provide a description of specific patient subpopulations in which the product is expected to be most effective, if known. Include clinical markers, diagnostic or genetic criteria, or other markers, if known, that can be used to identify these subpopulations. When possible, this information should reflect a population of US patients. Present a summary of information from the literature for topics, including, but not be limited to:

1. Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product.
2. Pathophysiology.
3. Clinical presentation.
4. Societal, humanistic, and economic burden.
5. Health disparities related to social and demographic factors such as race, gender, income, or geographic region.

This section may be expanded to provide greater detail for medications and other treatments that require intense clinical monitoring to manage severe side effects, frequent dose adjustments, or specialized training for handling and administration. For example, this section may be expanded for products that are used to treat rare diseases for which relatively little information may be available in the public domain. Likewise, expanded information is useful for products that are costly, have few competing or generic alternatives, or have limited distribution or access points.

2.2.2 B APPROACHES TO TREATMENT

The key questions to address are: How is the disease/condition currently treated? If known, how does the product fit into existing therapeutic algorithms? The unmet need should be highlighted when data are available. These data may not be available for new products but should be included for legacy products.

Provide a summary of information but **do not duplicate information included in other sections. Use hyperlinks to other sections vs. repeating.**

1. Summarize current approaches to treatment (drug and nondrug), including where this product fits in with existing therapies and fulfills unmet needs. When guidelines are also discussed in Section 5.1B, hyperlinking between the two sections is recommended.
2. Describe the place and anticipated uses of the product for treating disease, especially for certain subpopulations that can be targeted for the use of the product. This may include registry, RWE, clinical trial, or other information from competing products that provide information about the disease state or approaches to treatment. This should include whether the product addresses unmet needs, including those related to health disparities.
3. Describe heterogeneity of treatment effect, if any, related to the use of the product. Hyperlink to Section 3.0 for specific findings. Response to therapy may vary from patient to patient. Any information that substantiates heterogeneity effects (benefit and harms) of the proposed therapy should be described here and supported with evidence from studies in Section 3.0B (e.g., crossover study designs, N-of-1 studies, subgroup analyses).
4. Include proposed ancillary disease or care management intervention strategies provided by the manufacturer that are intended to accompany the product at launch. Services intended to accompany a specialty pharmaceutical at launch should be described. These may include any of the following: patient education services, nursing administration support services, programs intended to promote adherence, coordination of information among providers or facilities, sharps disposal, and financial assistance to patients. Specific claims made regarding the benefits of these services should be documented in this section and supported by scientific evidence described in this section or reported in Section 3.0B or 5.0B if applicable. It should be clearly stated when there is no scientific evidence to support claims of benefits for these services. For patient assistance programs, it is optimal to include the terms of the program and the expected number of beneficiaries.
5. Describe other product development or post-marketing obligations as required by the FDA such as a REMS, phase 4 trial, patient registry, restricted distribution channel, and other elements designed to assure the safe use of the product. In addition to the existing instructions for this section, if a multifaceted program intended to accompany the product at launch will include REMS alongside other elements, describe it in section 2.2.2B(5) and note in 2.2.2B(6) that the program contains a REMS component.

6. Describe ongoing post-approval monitoring of drug safety and adverse events. Ongoing post-approval monitoring and cost of adverse events for newly approved products should be conducted and included, if available or if applicable. Signals of adverse events indicating disproportional rates of events should be reported. The estimated cost of adverse events, including the cost of monitoring, hospitalizations, emergency room visits, and any other relevant costs associated with treating the adverse event should be included. In addition, the health care decision-maker should contact the drug company for current additional information related to drug safety and adverse events.
7. Describe the key expected outcomes of therapy of the product. Hyperlink to Section 3.0 for specific findings.
8. Other key assumptions and their rationale.

3.0B CLINICAL EVIDENCE

Section 3.0B should consist of clinical studies that support the use and value of the product in a clear and concise format.

It is important that Section 3.0 is transparent and reflects the full body of clinical evidence that exists for a product. For a new product, available evidence may be limited to a few studies, and inclusion of all studies in the dossier is sensible. For a product that has been available for several years, there may be a very large number of studies in the medical literature and inclusion of every study may be impractical for both manufacturers and HCDMs. In such cases, it is important that the manufacturer exhibit transparency and fair representation concerning the evidence included in the dossier, while at the same time providing a dossier that is useful and manageable for HCDMs. Therefore, it is recommended that in such cases, the evidence be separated into the following categories:

1. An overview of information contained in Chapter 3.0 should be provided on page 1.
2. Pivotal data, and in some instances other RCTs and/or RWE, that contribute significantly to the knowledge base of the product should be included as study summaries **and** evidence tables.
3. Informative but smaller and/or less rigorous studies that may add to the evidence base should be included as **evidence tables only**.
4. All other studies that have been reported but do not add significantly to the knowledge base of the product should be identified in a **bibliography only**.

The overview of the information contained in Chapter 3.0 should define a specific set of objective criteria for inclusion and exclusion of studies and describe how studies were selected for inclusion and exclusion in this section. Studies excluded do not need to be identified in a bibliography. Considerations for establishing inclusion or exclusion criteria can be based on the study characteristics as is done in clinicaltrials.gov. These characteristics include but are not limited to, study design, number of subjects, and location of the study. In this section, the manufacturer should clearly explain the objective rationale for delineation and assignment of studies into each of the categories above to avoid selection bias. As these definitions may vary depending on the context of the product, clinical setting, and available treatment alternatives (e.g., common disorder vs. orphan disease), the manufacturer should justify how studies are included (study summaries vs. evidence tables vs. bibliography).

This section should also explain the degree to which study subjects represent the target population as described in 2.2.1 B Disease Description and identify differences that may obscure translation to real-world effectiveness. For clinical trials, the diversity of study participants should be explained and supplemental tables depicting trial representativeness are strongly encouraged. Retrospective studies should include subgroups disproportionately affected by the health condition, and data limitations that erode generalizability should be disclosed.

Considerations for Chapter 3.0:

- The length and level of detail for study summaries and evidence tables may vary based on the amount of available data. It must be noted that HCDMs want concise, focused, and user-friendly presentation of data. One of the most common complaints from HCDMs is that dossiers are too long.
- Specific study designs are not prescribed in this section. Manufacturers should include studies that generate evidence about clinical outcomes.
 - > Prospective clinical studies including RCTs, observational data, registries, real-world evidence, and other studies that measure clinical endpoints should generally be included in Chapter 3.0. Study results and outcomes may include efficacy, safety, tolerability, pharmacokinetics/ pharmacodynamics, patient preference, patient adherence, patient-reported outcomes, quality of life, evidence that identifies patient subgroups or clinical settings in which the product may be appropriate, and other clinically related outcomes.
 - > Retrospective studies, including real-world evidence, supporting the clinical use and clinical value of the product that are conducted using existing data from chart reviews, medical and pharmacy claims, electronic medical records, product and/or disease registries, patient-generated data including data gathered from other sources such as mobile applications, or other novel sources of data.
 - > In vitro, animal, and phase 1 studies are generally not included unless the value proposition is based on relevant pharmacologic, pharmacodynamics, or pharmacokinetic evidence in these earlier studies.
- Studies available from published medical journals are preferred. When publications are not available, medical congress abstracts, posters, and scientific podium presentations can be considered. Publicly available information from manuscripts submitted or accepted by medical journals, Clinicaltrials.gov, FDA briefing documents and manufacturers' data on file can also be used, when applicable.
- Comparative evidence is a necessary component of a comprehensive product dossier. For this reason, it is strongly recommended that head-to-head clinical studies between the product and its primary comparators be included in Chapter 3.0. In the absence of head-to-head data, other comparative efficacy and safety analyses may be considered.
- If the results of a trial have been reported in more than one journal article or conference abstract, poster, or oral presentation, all may be combined into one summary and one row of an evidence table, citing all the sources from which data have been drawn and clearly stating the total number of subjects. Discuss important study findings and comment on their implications for different patient populations.

- Potential off-label uses are of significant interest to HCDMs. As such, clinical studies involving off-label uses should be included in dossiers. Manufacturers should clearly delineate evidence for on- and off-label uses (i.e., organize and report on-label indications and information first and off-label after). If data regarding off-label use have been submitted to the FDA for approval but the FDA decision was to deny the approval of the proposed new indication, then the FDA decision should be briefly summarized.
- For products with more than one approved indication, the pharmaceutical manufacturer should decide how studies for labeled indications should be presented. If the manufacturer decides to have separate dossiers for each approved indication, those requesting dossiers must be apprised of the existence of more than one dossier, and that each can only be supplied pursuant to an unsolicited request. In all cases, however, all studies for a given indication should be grouped together in the dossier.
- For pharmaceuticals designated by the FDA as “breakthrough drugs,” evidentiary reporting requirements are the same as for other drugs. For biosimilars, basic evidentiary needs are the same as for “traditional” and “specialty” pharmaceuticals. While it is recognized that trials dealing with interchangeability, dosing equivalency, comparison with innovator agents, etc. are especially important, all trials dealing with biosimilars should be reported since there is often limited data available for such products, and HCDMs need access to all relevant evidence and data.
- Data summarized in Chapter 3.0 should not be also summarized in 5.0.

FORMAT OF THE *FORMAT*

QUESTION 7: FORMAT OF THE *FORMAT*

- From an efficiency standpoint, we are proposing to use external hyperlinks for product information, websites, and guidelines. How would this affect your resources?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Approved Product Dossiers, Sections 2.1B, 2.2B and 3.0B

**Proposed revisions are highlighted in yellow.*

2.0 B PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 B PRODUCT DESCRIPTION

The recommended length of Section 2.1B is five pages (maximum 10). This section can be written in paragraph or as a **table (preferred)**. Brevity should be considered when writing this section. When possible, use language from the highlights section of the USPI or hyperlink to the USPI.

Basic product information should generally be provided, including but not limited to:

- Generic name
- Brand name
- FDA-approved indication(s) and approval date
- Therapeutic class
- Dosage forms and strengths
- Contraindications
- Boxed Warning
- Warnings/Precautions
- Adverse events
- Unique Device Identifiers (e.g. NDC number, AHFS)
- Wholesale acquisition cost (WAC) pricing

Other differentiating attributes may also be included, when clinically necessary.

- Pharmacology (MOA/pharmacokinetics/pharmacodynamics)
- Special populations (e.g., pregnancy, pediatric use, renal impairment).
- Drug/drug, drug/food, and drug disease interactions
- Access (e.g., restrictions on distribution, supply limitations, anticipated shortages, patient assistance, and prescribing restrictions).
- Product development or post-marketing obligations as required by the FDA .
- Post-approval monitoring of drug safety and adverse events.
- Co-prescribed/concomitant therapies

Additional information beyond the label should only be provided in cases where one or more of these attributes is of major significance in defining the value of a product.

Table of Highlights for Digital Therapeutics

Type of Information	Description of Information
Product version	Include version of application that the dossier applies to
Approval pathway	FDA clearance, class II device, predicates based on the desktop app now transferred to the web, etc.
Intended environment of therapy delivery and ongoing use	<ul style="list-style-type: none"> • Patient setting (home, work, school) • Healthcare setting • Institutional setting (nursing home, long-term care)
Intended line of business	<ul style="list-style-type: none"> • Commercial, Medicare, Medicaid
Relationship to other therapies	<ul style="list-style-type: none"> • Standalone • Add-on therapy to standard of care • Replaces existing therapy • Co-prescribed with pharmacologic therapy
Language	<ul style="list-style-type: none"> • Languages the product is available in
Considerations for specific populations	<ul style="list-style-type: none"> • Additional information on cultural, disability, age, health or digital literacy requirements

Type of Information	Description of Information
Patient access to the product	<ul style="list-style-type: none"> • Formal prescription from a qualified clinician (in-person or virtual engagement) • Clinician referral for a non-prescription DTx product (in-person or virtual engagement) • Direct authorization by an employer for a non-prescription DTx product • Direct authorization by a payor for a non-prescription DTx product • “Authorized clinical protocol” established by a HCDM to authorize automatic patient access when necessary, qualification requirements are met • “Clinically validated screening tool” that patients use to determine whether they qualify for the therapy » “Over-the-counter” model where no form of third-party authorization is necessary • Details on the dispensing process may also be included (e.g., download, specialty pharmacy, etc.)
Components required for the software to deliver its therapeutic value	Additional hardware or software required
Host technology and required hardware components (if applicable)	Smartphone, tablet, laptop, wearable device
Technical requirements	<ul style="list-style-type: none"> • Offline-capable • Broadband
Compatibility	<ul style="list-style-type: none"> • PC/MAC • Browser (Chrome, Edge, Safari) • iOS • Android
Technical assistance availability	Is there in-app support via chat or call center availability.

2.1.1 B PRODUCT COMPARISON

A statement as to why the comparators were selected should be included (e.g., meta-analyses, guidelines, literature search). If comparator products are selected based on guidelines, it may be necessary to include information from the guidelines in the product comparison table.

Concise comparison of PI information with the primary comparator products in the same therapeutic area, generally including, but not limited to indications, contraindications, dosing, boxed warning, warning/precaution, AEs, and other differentiating characteristics (expand as appropriate for the therapeutic class). This information should generally come from the highlights section of the USPI.

If direct head-to-head trials have been conducted comparing the product to its comparators, this should be noted here, and the reader referred to the review of those trials in Section 3.0B of the dossier.

For biosimilar products, comparator information about the reference product should be included as well as evidence that demonstrates biosimilarity or interchangeability.

2.2 B PLACE OF THE PRODUCT IN THERAPY

The recommended length of Section 2.2B is 5 pages (maximum 10) for each indication.

Information presented in this section should be brief. Do not duplicate information presented in Sections 3.0B, 4.0B, and 5.0B. Hyperlinks within the document can be useful to encourage brevity when possible.

2.2.1 B DISEASE DESCRIPTION

The disease description should be a **top-line overview** focusing on the specific patient populations for which the product is indicated or seeking an indication.

Manufacturers should provide a description of specific patient subpopulations in which the product is expected to be most effective, if known. Include clinical markers, diagnostic or genetic criteria, or other markers, if known, that can be used to identify these subpopulations. When possible, this information should reflect a population of US patients. Present a summary of information from the literature for topics, including, but not be limited to:

1. Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product.
2. Pathophysiology.
3. Clinical presentation.
4. Societal, humanistic, and economic burden.
5. Health disparities related to social and demographic factors such as race, gender, income, or geographic region.

This section may be expanded to provide greater detail for medications and other treatments that require intense clinical monitoring to manage severe side effects, frequent dose adjustments, or specialized training for handling and administration. For example, this section may be expanded for products that are used to treat rare diseases for which relatively little information may be available in the public domain. Likewise, expanded information is useful for products that are costly, have few competing or generic alternatives, or have limited distribution or access points.

2.2.2 B APPROACHES TO TREATMENT

The key questions to address are: How is the disease/condition currently treated?

If known, how does the product fit into existing therapeutic algorithms? The unmet need should be highlighted when data are available. These data may not be available for new products but should be included for legacy products.

Provide a summary of information but **do not duplicate information included in other sections. Use hyperlinks to other sections vs. repeating.**

1. Summarize current approaches to treatment (drug and nondrug), including where this product fits in with existing therapies and fulfills unmet needs. When guidelines are also discussed in Section 5.1B, hyperlinking between the two sections is recommended.
2. Describe the place and anticipated uses of the product for treating disease, especially for certain subpopulations that can be targeted for the use of the product. This may include registry, RWE, clinical trial, or other information from competing products that provide information about the disease state or approaches to treatment. This should include whether the product addresses unmet needs, including those related to health disparities.
3. Describe heterogeneity of treatment effect, if any, related to the use of the product. Hyperlink to Section 3.0 for specific findings. Response to therapy may vary from patient to patient. Any information that substantiates heterogeneity effects (benefit and harms) of the proposed therapy should be described here and supported with evidence from studies in Section 3.0B (e.g., crossover study designs, N-of-1 studies, subgroup analyses).
4. Include proposed ancillary disease or care management intervention strategies provided by the manufacturer that are intended to accompany the product at launch. Services intended to accompany a specialty pharmaceutical at launch should be described. These may include any of the following: patient education services, nursing administration support services, programs intended to promote adherence, coordination of information among providers or facilities, sharps disposal, and financial assistance to patients. Specific claims made regarding the benefits of these services should be documented in this section and supported by scientific evidence described in this section or reported in Section 3.0B or 5.0B if applicable. It should be clearly stated when there is no scientific evidence to support claims of benefits for these services. For patient assistance programs, it is optimal to include the terms of the program and the expected number of beneficiaries.
5. Describe other product development or post-marketing obligations as required by the FDA such as a REMS, phase 4 trial, patient registry, restricted distribution channel, and other elements designed to assure the safe use of the product. In addition to the existing instructions for this section, if a multifaceted program intended to accompany the product at launch will include REMS alongside other elements, describe it in section 2.2.2B(5) and note in 2.2.2B(6) that the program contains a REMS component.

6. Describe ongoing post-approval monitoring of drug safety and adverse events. Ongoing post-approval monitoring and cost of adverse events for newly approved products should be conducted and included, if available or if applicable. Signals of adverse events indicating disproportional rates of events should be reported. The estimated cost of adverse events, including the cost of monitoring, hospitalizations, emergency room visits, and any other relevant costs associated with treating the adverse event should be included. In addition, the health care decision-maker should contact the drug company for current additional information related to drug safety and adverse events.
7. Describe the key expected outcomes of therapy of the product. [Hyperlink to Section 3.0 for specific findings.](#)
8. Other key assumptions and their rationale.

3.0B CLINICAL EVIDENCE

Section 3.0B should consist of clinical studies that support the use and value of the product in a clear and concise format.

It is important that Section 3.0 is transparent and reflects the full body of clinical evidence that exists for a product. For a new product, available evidence may be limited to a few studies, and inclusion of all studies in the dossier is sensible. For a product that has been available for several years, there may be a very large number of studies in the medical literature and inclusion of every study may be impractical for both manufacturers and HCDMs. In such cases, it is important that the manufacturer exhibit transparency and fair representation concerning the evidence included in the dossier, while at the same time providing a dossier that is useful and manageable for HCDMs. Therefore, it is recommended that in such cases, the evidence be separated into the following categories:

1. An overview of information contained in Chapter 3.0 should be provided on page 1.
2. Pivotal data, and in some instances other RCTs and/or RWE, that contribute significantly to the knowledge base of the product should be included as study summaries **and** evidence tables.
3. Informative but smaller and/or less rigorous studies that may add to the evidence base should be included as **evidence tables only**.
4. All other studies that have been reported but do not add significantly to the knowledge base of the product should be identified in a **bibliography only**.

The overview of the information contained in Chapter 3.0 should define a specific set of objective criteria for inclusion and exclusion of studies and describe how studies were selected for inclusion and exclusion in this section. Studies excluded do not need to be identified in a bibliography. Considerations for establishing inclusion or exclusion criteria can be based on the study characteristics as is done in clinicaltrials.gov. These characteristics include but are not limited to, study design, number of subjects, and location of the study. In this section, the manufacturer should clearly explain the objective rationale for delineation and assignment of studies into each of the categories above to avoid selection bias. As these definitions may vary depending on the context of the product, clinical setting, and available treatment alternatives (e.g., common disorder vs. orphan disease), the manufacturer should justify how studies are included (study summaries vs. evidence tables vs. bibliography).

This section should also explain the degree to which study subjects represent the target population as described in 2.2.1 B Disease Description, and identify differences that may obscure translation to real-world effectiveness. For clinical trials, the diversity of study participants should be explained and supplemental tables depicting trial representativeness are strongly encouraged. Retrospective studies should include subgroups disproportionately affected by the health condition, and data limitations that erode generalizability should be disclosed.

Considerations for Chapter 3.0:

- The length and level of detail for study summaries and evidence tables may vary based on the amount of available data. It must be noted that HCDMs want concise, focused, and user-friendly presentation of data. One of the most common complaints from HCDMs is that dossiers are too long.
- Specific study designs are not prescribed in this section. Manufacturers should include studies that generate evidence about clinical outcomes.
 - > Prospective clinical studies including RCTs, observational data, registries, real-world evidence, and other studies that measure clinical endpoints should generally be included in Chapter 3.0. Study results and outcomes may include efficacy, safety, tolerability, pharmacokinetics/pharmacodynamics, patient preference, patient adherence, patient-reported outcomes, quality of life, evidence that identifies patient subgroups or clinical settings in which the product may be appropriate, and other clinically related outcomes.
 - > Retrospective studies, including real-world evidence, supporting the clinical use and clinical value of the product that are conducted using existing data from chart reviews, medical and pharmacy claims, electronic medical records, product and/or disease registries, patient-generated data including data gathered from other sources such as mobile applications, or other novel sources of data.
 - > In vitro, animal, and phase 1 studies are generally not included unless the value proposition is based on relevant pharmacologic, pharmacodynamics, or pharmacokinetic evidence in these earlier studies.
- Studies available from published medical journals are preferred. When publications are not available, medical congress abstracts, posters, and scientific podium presentations can be considered. Publicly available information from manuscripts submitted or accepted by medical journals, Clinicaltrials.gov, FDA briefing documents and manufacturers' data on file can also be used, when applicable.
- Comparative evidence is a necessary component of a comprehensive product dossier. For this reason, it is strongly recommended that head-to-head clinical studies between the product and its primary comparators be included in Chapter 3.0. In the absence of head-to-head data, other comparative efficacy and safety analyses may be considered.
- If the results of a trial have been reported in more than one journal article or conference abstract, poster, or oral presentation, all may be combined into one summary and one row of an evidence table, citing all the sources from which data have been drawn and clearly stating the total number of subjects. Discuss important study findings and comment on their implications for different patient populations.

- Potential off-label uses are of significant interest to HCDMs. As such, clinical studies involving off-label uses should be included in dossiers. Manufacturers should clearly delineate evidence for on- and off-label uses (i.e., organize and report on-label indications and information first and off-label after). If data regarding off-label use have been submitted to the FDA for approval but the FDA decision was to deny the approval of the proposed new indication, then the FDA decision should be briefly summarized.
- For products with more than one approved indication, the pharmaceutical manufacturer should decide how studies for labeled indications should be presented. If the manufacturer decides to have separate dossiers for each approved indication, those requesting dossiers must be apprised of the existence of more than one dossier, and that each can only be supplied pursuant to an unsolicited request. In all cases, however, all studies for a given indication should be grouped together in the dossier.
- For pharmaceuticals designated by the FDA as “breakthrough drugs,” evidentiary reporting requirements are the same as for other drugs. For biosimilars, basic evidentiary needs are the same as for “traditional” and “specialty” pharmaceuticals. While it is recognized that trials dealing with interchangeability, dosing equivalency, comparison with innovator agents, etc. are especially important, all trials dealing with biosimilars should be reported since there is often limited data available for such products, and HCDMs need access to all relevant evidence and data.
- Data summarized in Chapter 3.0 should not be also summarized in 5.0.

FORMAT OF THE *FORMAT*

QUESTION 8: FORMAT OF THE *FORMAT*

- Information regarding digital therapeutics was added to the dossier. Are there any other categories of products for which specific guidance would be helpful?

SECTIONS WITH PROPOSED REVISIONS:

- Evidence Recommendations for Approved Product Dossiers, Sections 2.1B, 2.2B and 3.0B

**Proposed revisions are highlighted in yellow.*

2.0 B PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 B PRODUCT DESCRIPTION

The recommended length of Section 2.1B is five pages (maximum 10). This section can be written in paragraph or as a table (preferred). Brevity should be considered when writing this section. When possible, use language from the highlights section of the USPI or hyperlink to the USPI.

Basic product information should generally be provided, including but not limited to:

- Generic name
- Brand name
- FDA-approved indication(s) and approval date
- Therapeutic class
- Dosage forms and strengths
- Contraindications
- Boxed Warning
- Warnings/Precautions
- Adverse events
- Unique Device Identifiers (e.g. NDC number, AHFS)
- Wholesale acquisition cost (WAC) pricing

Other differentiating attributes may also be included, when clinically necessary.

- Pharmacology (MOA/pharmacokinetics/pharmacodynamics)
- Special populations (e.g., pregnancy, pediatric use, renal impairment).
- Drug/drug, drug/food, and drug disease interactions
- Access (e.g., restrictions on distribution, supply limitations, anticipated shortages, patient assistance, and prescribing restrictions).
- Product development or post-marketing obligations as required by the FDA .
- Post-approval monitoring of drug safety and adverse events.
- Co-prescribed/concomitant therapies

Additional information beyond the label should only be provided in cases where one or more of these attributes is of major significance in defining the value of a product.

Table of Highlights for Digital Therapeutics

<i>Type of Information</i>	<i>Description of Information</i>
Product version	Include version of application that the dossier applies to
Approval pathway	FDA clearance, class II device, predicates based on the desktop app now transferred to the web, etc.
Intended environment of therapy delivery and ongoing use	<ul style="list-style-type: none"> • Patient setting (home, work, school) • Healthcare setting • Institutional setting (nursing home, long-term care)
Intended line of business	<ul style="list-style-type: none"> • Commercial, Medicare, Medicaid
Relationship to other therapies	<ul style="list-style-type: none"> • Standalone • Add-on therapy to standard of care • Replaces existing therapy • Co-prescribed with pharmacologic therapy
Language	<ul style="list-style-type: none"> • Languages the product is available in
Considerations for specific populations	<ul style="list-style-type: none"> • Additional information on cultural, disability, age, health or digital literacy requirements

Type of Information	Description of Information
Patient access to the product	<ul style="list-style-type: none"> • Formal prescription from a qualified clinician (in-person or virtual engagement) • Clinician referral for a non-prescription DTx product (in-person or virtual engagement) • Direct authorization by an employer for a non-prescription DTx product • Direct authorization by a payor for a non-prescription DTx product • “Authorized clinical protocol” established by a HCDM to authorize automatic patient access when necessary, qualification requirements are met • “Clinically validated screening tool” that patients use to determine whether they qualify for the therapy » “Over-the-counter” model where no form of third-party authorization is necessary • Details on the dispensing process may also be included (e.g., download, specialty pharmacy, etc.)
Components required for the software to deliver its therapeutic value	Additional hardware or software required
Host technology and required hardware components (if applicable)	Smartphone, tablet, laptop, wearable device
Technical requirements	<ul style="list-style-type: none"> • Offline-capable • Broadband
Compatibility	<ul style="list-style-type: none"> • PC/MAC • Browser (Chrome, Edge, Safari) • iOS • Android
Technical assistance availability	Is there in-app support via chat or call center availability.

2.1.1 B PRODUCT COMPARISON

A statement as to why the comparators were selected should be included (e.g., meta-analyses, guidelines, literature search). If comparator products are selected based on guidelines, it may be necessary to include information from the guidelines in the product comparison table.

Concise comparison of PI information with the primary comparator products in the same therapeutic area, generally including, but not limited to indications, contraindications, dosing, boxed warning, warning/precaution, AEs, and other differentiating characteristics (expand as appropriate for the therapeutic class). This information should generally come from the highlights section of the USPI.

If direct head-to-head trials have been conducted comparing the product to its comparators, this should be noted here, and the reader referred to the review of those trials in Section 3.0B of the dossier.

For biosimilar products, comparator information about the reference product should be included as well as evidence that demonstrates biosimilarity or interchangeability.

2.2 B PLACE OF THE PRODUCT IN THERAPY

The recommended length of Section 2.2B is 5 pages (maximum 10) for each indication.

Information presented in this section should be brief. Do not duplicate information presented in Sections 3.0B, 4.0B, and 5.0B. Hyperlinks within the document can be useful to encourage brevity when possible.

2.2.1 B DISEASE DESCRIPTION

The disease description should be a **top-line overview** focusing on the specific patient populations for which the product is indicated or seeking an indication.

Manufacturers should provide a description of specific patient subpopulations in which the product is expected to be most effective, if known. Include clinical markers, diagnostic or genetic criteria, or other markers, if known, that can be used to identify these subpopulations. When possible, this information should reflect a population of US patients. Present a summary of information from the literature for topics, including, but not be limited to:

1. Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product.
2. Pathophysiology.
3. Clinical presentation.
4. Societal, humanistic, and economic burden.
5. Health disparities related to social and demographic factors such as race, gender, income, or geographic region.

This section may be expanded to provide greater detail for medications and other treatments that require intense clinical monitoring to manage severe side effects, frequent dose adjustments, or specialized training for handling and administration. For example, this section may be expanded for products that are used to treat rare diseases for which relatively little information may be available in the public domain. Likewise, expanded information is useful for products that are costly, have few competing or generic alternatives, or have limited distribution or access points.

2.2.2 B APPROACHES TO TREATMENT

The key questions to address are: How is the disease/condition currently treated?

If known, how does the product fit into existing therapeutic algorithms? The unmet need should be highlighted when data are available. These data may not be available for new products but should be included for legacy products.

Provide a summary of information but **do not duplicate information included in other sections.**

Use hyperlinks to other sections vs. repeating.

1. Summarize current approaches to treatment (drug and nondrug), including where this product fits in with existing therapies and fulfills unmet needs. When guidelines are also discussed in Section 5.1B, hyperlinking between the 2 sections is recommended.
2. Describe the place and anticipated uses of the product for treating disease, especially for certain subpopulations that can be targeted for the use of the product. This may include registry, RWE, clinical trial, or other information from competing products that provide information about the disease state or approaches to treatment. This should include whether the product addresses unmet needs, including those related to health disparities.
3. Describe heterogeneity of treatment effect, if any, related to the use of the product. Hyperlink to Section 3.0 for specific findings. Response to therapy may vary from patient to patient. Any information that substantiates heterogeneity effects (benefit and harms) of the proposed therapy should be described here and supported with evidence from studies in Section 3.0B (e.g., crossover study designs, N-of-1 studies, subgroup analyses).
4. Include proposed ancillary disease or care management intervention strategies provided by the manufacturer that are intended to accompany the product at launch. Services intended to accompany a specialty pharmaceutical at launch should be described. These may include any of the following: patient education services, nursing administration support services, programs intended to promote adherence, coordination of information among providers or facilities, sharps disposal, and financial assistance to patients. Specific claims made regarding the benefits of these services should be documented in this section and supported by scientific evidence described in this section or reported in Section 3.0B or 5.0B if applicable. It should be clearly stated when there is no scientific evidence to support claims of benefits for these services. For patient assistance programs, it is optimal to include the terms of the program and the expected number of beneficiaries.
5. Describe other product development or post-marketing obligations as required by the FDA such as a REMS, phase 4 trial, patient registry, restricted distribution channel, and other elements designed to assure the safe use of the product. In addition to the existing instructions for this section, if a multifaceted program intended to accompany the product at launch will include REMS alongside other elements, describe it in section 2.2.2B(5) and note in 2.2.2B(6) that the program contains a REMS component.

6. Describe ongoing post-approval monitoring of drug safety and adverse events. Ongoing post-approval monitoring and cost of adverse events for newly approved products should be conducted and included, if available or if applicable. Signals of adverse events indicating disproportional rates of events should be reported. The estimated cost of adverse events, including the cost of monitoring, hospitalizations, emergency room visits, and any other relevant costs associated with treating the adverse event should be included. In addition, the health care decision-maker should contact the drug company for current additional information related to drug safety and adverse events.
7. Describe the key expected outcomes of therapy of the product. [Hyperlink to Section 3.0 for specific findings.](#)
8. Other key assumptions and their rationale.

3.0B CLINICAL EVIDENCE

Section 3.0B should consist of clinical studies that support the use and value of the product in a clear and concise format.

It is important that Section 3.0 is transparent and reflects the full body of clinical evidence that exists for a product. For a new product, available evidence may be limited to a few studies, and inclusion of all studies in the dossier is sensible. For a product that has been available for several years, there may be a very large number of studies in the medical literature and inclusion of every study may be impractical for both manufacturers and HCDMs. In such cases, it is important that the manufacturer exhibit transparency and fair representation concerning the evidence included in the dossier, while at the same time providing a dossier that is useful and manageable for HCDMs. Therefore, it is recommended that in such cases, the evidence be separated into the following categories:

1. An overview of information contained in Chapter 3.0 should be provided on page 1.
2. Pivotal data, and in some instances other RCTs and/or RWE, that contribute significantly to the knowledge base of the product should be included as study summaries **and** evidence tables.
3. Informative but smaller and/or less rigorous studies that may add to the evidence base should be included as **evidence tables only**.
4. All other studies that have been reported but do not add significantly to the knowledge base of the product should be identified in a **bibliography only**.

The overview of the information contained in Chapter 3.0 should define a specific set of objective criteria for inclusion and exclusion of studies and describe how studies were selected for inclusion and exclusion in this section. Studies excluded do not need to be identified in a bibliography. Considerations for establishing inclusion or exclusion criteria can be based on the study characteristics as is done in [clinicaltrials.gov](#). These characteristics include but are not limited to, study design, number of subjects, and location of the study. In this section, the manufacturer should clearly explain the objective rationale for delineation and assignment of studies into each of the categories above to avoid selection bias. As these definitions may vary depending on the context of the product, clinical setting, and available treatment alternatives (e.g., common disorder vs. orphan disease), the manufacturer should justify how studies are included (study summaries vs. evidence tables vs. bibliography).

This section should also explain the degree to which study subjects represent the target population as described in 2.2.1 B Disease Description, and identify differences that may obscure translation to real-world effectiveness. For clinical trials, the diversity of study participants should be explained and supplemental tables depicting trial representativeness are strongly encouraged. Retrospective studies should include subgroups disproportionately affected by the health condition, and data limitations that erode generalizability should be disclosed.

Considerations for Chapter 3.0:

- The length and level of detail for study summaries and evidence tables may vary based on the amount of available data. It must be noted that HCDMs want concise, focused, and user-friendly presentation of data. One of the most common complaints from HCDMs is that dossiers are too long.
- Specific study designs are not prescribed in this section. Manufacturers should include studies that generate evidence about clinical outcomes.
 - > Prospective clinical studies including RCTs, observational data, registries, real-world evidence, and other studies that measure clinical endpoints should generally be included in Chapter 3.0. Study results and outcomes may include efficacy, safety, tolerability, pharmacokinetics/ pharmacodynamics, patient preference, patient adherence, patient-reported outcomes, quality of life, evidence that identifies patient subgroups or clinical settings in which the product may be appropriate, and other clinically related outcomes.
 - > Retrospective studies, including real-world evidence, supporting the clinical use and clinical value of the product that are conducted using existing data from chart reviews, medical and pharmacy claims, electronic medical records, product and/or disease registries, patient-generated data including data gathered from other sources such as mobile applications, or other novel sources of data.
 - > In vitro, animal, and phase 1 studies are generally not included unless the value proposition is based on relevant pharmacologic, pharmacodynamics, or pharmacokinetic evidence in these earlier studies.
- Studies available from published medical journals are preferred. When publications are not available, medical congress abstracts, posters, and scientific podium presentations can be considered. Publicly available information from manuscripts submitted or accepted by medical journals, Clinicaltrials.gov, FDA briefing documents and manufacturers' data on file can also be used, when applicable.
- Comparative evidence is a necessary component of a comprehensive product dossier. For this reason, it is strongly recommended that head-to-head clinical studies between the product and its primary comparators be included in Chapter 3.0. In the absence of head-to-head data, other comparative efficacy and safety analyses may be considered.
- If the results of a trial have been reported in more than one journal article or conference abstract, poster, or oral presentation, all may be combined into one summary and one row of an evidence table, citing all the sources from which data have been drawn and clearly stating the total number of subjects. Discuss important study findings and comment on their implications for different patient populations.

- Potential off-label uses are of significant interest to HCDMs. As such, clinical studies involving off-label uses should be included in dossiers. Manufacturers should clearly delineate evidence for on- and off-label uses (i.e., organize and report on-label indications and information first and off-label after). If data regarding off-label use have been submitted to the FDA for approval but the FDA decision was to deny the approval of the proposed new indication, then the FDA decision should be briefly summarized.
- For products with more than one approved indication, the pharmaceutical manufacturer should decide how studies for labeled indications should be presented. If the manufacturer decides to have separate dossiers for each approved indication, those requesting dossiers must be apprised of the existence of more than one dossier, and that each can only be supplied pursuant to an unsolicited request. In all cases, however, all studies for a given indication should be grouped together in the dossier.
- For pharmaceuticals designated by the FDA as “breakthrough drugs,” evidentiary reporting requirements are the same as for other drugs. For biosimilars, basic evidentiary needs are the same as for “traditional” and “specialty” pharmaceuticals. While it is recognized that trials dealing with interchangeability, dosing equivalency, comparison with innovator agents, etc. are especially important, all trials dealing with biosimilars should be reported since there is often limited data available for such products, and HCDMs need access to all relevant evidence and data.
- Data summarized in Chapter 3.0 should not be also summarized in 5.0.

PIE DECK GUIDANCE

QUESTION 9: PIE DECK GUIDANCE

- Does this section accurately represent key considerations for pre-approval information exchange (PIE) decks?
- What other aspects of PIE decks would you like to see AMCP address in this proposed guidance?

SECTIONS WITH PROPOSED REVISIONS:

- New Appendix

**Proposed revisions are highlighted in yellow.*

PIE Deck Guidance

AMCP has a well-established history of supporting appropriate pre-approval information exchange (PIE) to provide opportunities for critical, early scientific dialogue regarding new treatments and new indications of existing treatments. As early as 2016 with the publication of the AMCP *Format v. 4.0*, the AMCP *Format* has addressed this need.¹ More recently, AMCP *Format v. 4.1* provided detailed guidance for preapproval dossiers for unapproved products and unapproved uses.²

Today, many manufacturers have pursued preapproval information exchange with healthcare decision makers (HCDMs), using both the AMCP *Format* as well as other means including the use of PIE decks.³ These tools support useful bi-directional communication. Two external milestones have provided additional support for preapproval dialogue between manufacturers and HCDMs. In 2018, the FDA published guidance on appropriate communications among manufacturers and payors, including PIE.

¹ AMCP. The AMCP *Format for Formulary Submissions* (version 4.0). April 2016. Available at: <http://www.amcp.org/FormatV4/>. Accessed May 17, 2023.

² AMCP. The AMCP *Format for Formulary Submissions* (version 4.0). January 2020. Available at: <https://www.amcp.org/Resource-Center/format-formulary-submissions/AMCP-Format-for-Formulary-Submissions-4.1>. Accessed May 17, 2023.

³ Dodda S, Bannister B, Hyderey H, et al. Best practices in designing preapproval information engagements for US health care decision makers. *J Manag Care Spec Pharm*, 2023 Mar;29(3):245-250. Available at: <https://doi.org/10.18553/jmcp.2023.29.3.245>. Accessed May 17, 2023.

Secondly, the “PIE Act” was passed in December 2022, amending the Federal Food, Drug, and Cosmetic Act to provide explicit legal protection to manufacturers conveying certain information about products in development to HCDMs, including unapproved uses of approved products.^{4,5}

AMCP applauds the passage of the PIE Act and recognizes the important balance of maintaining flexibility for manufacturer communications with HCDM needs. Notwithstanding the vehicle for pre-approval communications, AMCP urges manufacturers to keep HCDM priorities in mind and provide accurate, balanced, scientific information that is transparent in its disclosure of limitations and uncertainties. This will help enable payor decision-making, ultimately expediting patient access to new, needed medications. While the AMCP Format is a more holistic approach to conveying pre-approval product information, AMCP supports the use of PIE decks as another alternative that aligns with the goals of the PIE Act.

Given the importance of PIE to HCDMs in carrying out their responsibilities regarding budget forecasting, formulary decision-making, and facilitating patient access, manufacturers should prioritize early, meaningful communications about products expected to have significant impacts on organizational budgets. This may include products targeting a clinical area that previously did not have pharmacy treatment options, chronic disease states with high growth or prevalence, and those products with novel mechanisms of action. Because products in development will differ in terms of their budget impact to HCDMs, communication timelines and content should be tailored to reflect those impacts. The communication timeline could vary from six months up to two or more years prior to product approval, depending on product characteristics and potential budget impact.

Information included in PIE decks should include:

- Information from ongoing and completed trials.
 - > Unmet need/epidemiology
 - > Inclusion and exclusion criteria
 - > Study design and interventions
 - > Primary and secondary endpoints
 - > Known results
- Important timeline information
 - > Anticipated FDA submissions
 - > Expected approval and launch dates

⁴ H.R.2617—Consolidated Appropriations Act, 2023. Available at: <https://www.congress.gov/bill/117th-congress/house-bill/2617/text>. Accessed May 17, 2023.

⁵ 21 USC 352: Misbranded drugs and devices. Available at: <https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title21-section352&num=0&edition=prelim>. Accessed May 17, 2023.

- Information relevant to patient access
 - > Risk Evaluation and Mitigation Strategies (REMS)
 - > Limited or restricted distribution plans
 - > Anticipated limitations on pharmacies or administration sites
 - > Unusual monitoring or administration requirements (e.g., first-dose monitoring, novel observation procedures, prolonged administration times)

AMCP encourages a continuing dialogue between manufacturers and HCDMs as new information becomes available. Manufacturers should be mindful of prior communications with HCDMs and provide meaningful, timely updates as appropriate.