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AMCP Format for Formulary Submissions 5.0

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



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Publisher's Note

AMCP is pleased to provide this resource to its members and other stakeholders. As with previous versions of the *AMCP Format for Formulary Submissions (AMCP Format)*, updates to product dossiers are recommended whenever new information becomes available. However, the AMCP Format is not a mandate and instead serves as guidance to describe the information needs of health care decision-makers. Development and use of dossiers are at the discretion of the manufacturers and are subject to their individual legal and regulatory compliance policies.

Preface

The current need to evaluate and balance considerations related to clinical benefits, cost-effectiveness, and affordability has never been greater due to the development and availability of new health technologies and treatments that promise sustained durable effects and improved effectiveness.^{1,2} Since its initial release in 2000, the AMCP Format has provided a framework to advise manufacturers of important evidence needed by health care decision-makers (HCDMs) to evaluate new technologies for formulary and coverage consideration. The AMCP Format has been the basis for the development of dossiers by the industry to share clinical and economic evidence and information with HCDMs who make formulary and coverage decisions. While other value assessment frameworks exist,¹ the AMCP Format is designed to provide a comprehensive evidence framework that considers all sources of information for formulary decision-making by HCDMs. Dossiers developed and communicated based on the guidance in the AMCP Format are not considered promotional communications; rather, these dossiers are responsive to the needs of HCDMs in carrying out their responsibilities for the selection of products for coverage or reimbursement.

In 2020, the AMCP Format for Formulary Submissions Committee updated the AMCP Format to Version 4.1 to focus and modernize the bidirectional communication between manufacturers and HCDMs specifically as it relates to communication of pre-approval information.³

The AMCP Format Version 5.0 provides guidance on developing pre-approval information exchange (PIE) documents; addresses digital therapeutics (DTx), real-world evidence, and health disparities; and encourages brevity and streamlining of information throughout the dossier.

HCDMs need and are interested in receiving information from manufacturers about products seeking but having not

yet received United States Food and Drug Administration (FDA) approval (also known as pipeline or unapproved products) and unapproved uses of approved products for which FDA approval is being sought. This information assists HCDMs with their plans and budgets for future coverage and reimbursement decisions well before products and new uses are approved by the FDA. The FDA final guidance “Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities” (FDA Final Guidance) released in June 2018 acknowledges the needs of HCDMs to receive information about products in development.³ Although that guidance applies to manufacturer communications that may otherwise be considered “promotion,” the AMCP Format applies to the development and communication of dossiers that have generally been considered responsive to HCDM needs for evidence and information for population health care decision-making. In December 2022, the Pre-Approval Information Exchange Act of 2022 (PIE Act) was signed into law.⁴ This legislation provided a clinical framework by which pharmaceutical manufacturers could proactively communicate pre-approval information to HCDMs.

AMCP encourages the use of dossiers based on the AMCP Format Version 5.0 as a mechanism for manufacturers to communicate information about unapproved products, approved products, and unapproved uses of approved products to HCDMs. Dossiers based on the AMCP Format may serve as a continuously evolving source of objective, credible, and relevant information during the development and commercial life cycle of products.

To avoid confusion, throughout this document, the AMCP Format for Formulary Submissions Committee has adopted the terminology used in the FDA Final Guidance to describe the approval status of a product or indication: unapproved product, approved product, and unapproved use of an approved product for which FDA approval is being sought.

For manufacturers of drug products that have been selected for Medicare negotiation under the Inflation Reduction Act, there may be portions of this document that are useful for the provision of related information to the Centers for Medicare & Medicaid Services (CMS).⁵

Role of the AMCP Format

The evidentiary recommendations and guidelines outlined in the AMCP Format are intended for use by manufacturers to communicate clinical and economic evidence and information to HCDMs who make or influence formulary, coverage, policy, and reimbursement decisions for new and existing products. The AMCP Format is guidance, not a mandate. Manufacturers have final discretion on how to communicate information for consideration by HCDMs.

The AMCP Format supports the informed review, assessment, selection, and payment of medical products by:

- Identifying the evidence needed for evaluating the clinical and economic value of medical products.
- Standardizing the synthesis and organization of the evidence and information in a concise living document, known as the “AMCP dossier” or “product dossier,” that evolves with the life cycle of the product from the pre-approval phase through the post-approval period.
- Establishing a framework for the provision of objective and credible clinical and economic information needed by HCDMs.
- Recommending economic analyses and models to project the cost-effectiveness and budgetary impact on the HCDM’s organization and its patient or member population, as well as to assess the overall economic value of an approved product.
- Encouraging a clear and transparent bidirectional communication and sharing process between manufacturers and HCDMs.

The aim of the AMCP Format is to identify comprehensive evidence and information elements that meet the evidentiary needs of HCDMs. The AMCP Format is designed to encourage sharing of objective, credible, and relevant information on medical products. Specifically, the AMCP Format seeks to meet two important goals:

- Improve the timeliness, scope, quality, and relevance of clinical and economic evidence and information provided by manufacturers to HCDMs to enable HCDMs to assess and compare the clinical outcomes and economic consequences of a product relative to existing alternatives. The AMCP Format furnishes manufacturers with recommendations and guidelines on the nature and presentation of evidence and information expected.
- Streamline the evidence and information acquisition and review process for HCDMs. A product’s manufacturer may be a valuable source of evidence and information needed by HCDMs when planning for or assessing a product for formulary, coverage, policy, and reimbursement decisions. The standardized

presentation allows HCDMs to formally evaluate the completeness of submissions received and to easily add to the results of their own systematic literature reviews and analyses.

AMCP developed the AMCP Format as a template and guidance for developing dossiers, which have become among the most widely recognized standard source of clinical and economic evidence and information for HCDMs to request and receive from manufacturers for evaluating products. AMCP encourages manufacturers to develop and communicate dossiers according to the AMCP Format and for HCDMs to use dossiers in their product evaluation process. AMCP and the Format for Formulary Submissions Committee recognize that, while other organizations may release formats, guidelines, and value frameworks, the adoption and use of dossiers developed according to the AMCP Format should be regarded as a best practice for the formulary review process by health care organizations.

The AMCP Format provides recommendations for presenting evidence and information in a dossier that are necessary to support a comprehensive assessment of a medical product such as clinical benefit, safety, and economic impact. It is the manufacturer’s responsibility to convey such evidence and information in a truthful and nonmisleading way that meets currently accepted standards for evidence-based medicine and health technology assessment (HTA). Likewise, it is the HCDM’s responsibility to critically evaluate the evidence supplied according to currently accepted and published approaches to Pharmacy and Therapeutics (P&T) Committee review processes and formulary decision-making best practices, which have been reported in the literature.⁶⁻⁸ Submission of dossiers based on the AMCP Format by manufacturers to HCDMs does not guarantee positive decisions or formulary acceptance.

Since 2000, the AMCP Format has provided guidance to manufacturers on the development of approved product dossiers, which are communicated to HCDMs only by unsolicited requests (reactive communication), because these dossiers may contain information that extends beyond, and are sometimes inconsistent with, products’ prescribing information/package insert (PI) or FDA-approved labeling (i.e., any and all off-label uses). The increasing need for HCDMs to evaluate products before regulatory approval and market launch has long been a concern and has been recognized by the FDA and Congress.^{3,9} The AMCP Format Version 5.0 provides guidance on developing PIE resources and addressing DTx, real-world evidence, and health disparities, while encouraging brevity.

General Definitions And Considerations

This section defines certain key terms—dossier, health care decision-maker (HCDM), manufacturer, product, approval, communication between manufacturers and HCDMs, confidentiality, updating dossiers, dossier page limits, submission of dossiers, and pre-approval information exchange—that are used throughout the AMCP Format and provide certain logistical considerations on the development and communication of dossiers based on the AMCP Format.

Dossier

According to the AMCP Format, a “dossier” refers to a comprehensive and concise report containing clinical and economic evidence and information about a medical product that is developed and communicated by the manufacturer to HCDMs for the purpose of formulary, coverage, policy, and reimbursement decision-making.

In 2019, the AMCP Format Version 4.1¹⁰ expanded its recommendations to provide guidance on the development and communication of dossiers for unapproved products and unapproved uses of approved products for which FDA approval is being sought in order to meet HCDMs’ evidence and information needs, adding to the long-standing guidance for the traditional dossier for approved products.³ It is important to understand the characteristics of dossiers developed at different phases of a product’s life cycle and the rationale for such differences. However, it is also important to highlight that while HCDMs’ evidentiary needs are generally the same whenever they are reviewing and assessing products for formulary, coverage, policy, and reimbursement decisions, the type and amount of available evidence and information is dependent on the life cycle of the product (e.g., clinical development phase vs. post-marketing phase vs. loss of patent exclusivity). Thus, it is important to define the following:

1. *Unapproved Product Dossier*
 - Contains information about a product for which initial FDA approval will be or is being sought.
 - Is used by manufacturers to communicate information to HCDMs before FDA approval of the product.
2. *Approved Product Dossier*
 - Contains information about a product that has received FDA approval.
 - Is used by manufacturers to respond to unsolicited requests from HCDMs after FDA approval of the product (dossier contains on-label and any/all off-label information).
3. *Unapproved Use Dossier*
 - Contains information about off-label uses for which

the manufacturer is seeking FDA approval.

- Is used by manufacturers to communicate information to HCDMs about unapproved uses of an approved product for which the manufacturer is seeking FDA approval.

PRODUCT DOSSIER LIFE CYCLE

Product dossiers developed by manufacturers can be viewed as living documents that evolve and are updated when new evidence and information become available over the course of the product’s life cycle.

To illustrate, if the manufacturer chooses to develop an Unapproved Product Dossier, it is updated during the pre-approval period as evidence and information become available. At the time of FDA approval of the product, the manufacturer should retire the Unapproved Product Dossier by converting it to an Approved Product Dossier. The Approved Product Dossier is then updated throughout the post-approval period. An Unapproved Product Dossier and an Approved Product Dossier do not coexist during the product life cycle. See Figure 1.

Subsequently, the manufacturer may choose to develop an Unapproved Use Dossier during the post-approval period. The Unapproved Use Dossier is a separate document that the manufacturer may use to communicate information with HCDMs on an unapproved use for which the manufacturer is seeking FDA approval. While the Approved Product Dossier includes evidence and information about the approved uses and any and all unapproved uses that are supported by evidence, an Unapproved Use dossier only includes information on any and all unapproved uses for which FDA approval is being sought.³ The AMCP Format for Formulary Submissions Committee recognizes that the manufacturer may need to maintain two documents during the post-marketing period (e.g., the Approved Product Dossier containing all approved and unapproved information and the Unapproved Use Dossier containing information on only the unapproved use for which FDA approval is being sought). If there are multiple unapproved uses for which FDA approval is being sought, it is at the manufacturer’s discretion to include all unapproved uses in one Unapproved Use Dossier or develop separate Unapproved Use Dossiers for each unapproved use. Finally, once an unapproved use is approved by the FDA, the Approved Product Dossier should be updated, and the Unapproved Use Dossier should be retired for that use or updated by removing information for the newly approved use from the Unapproved Use Dossier.

TABLE 1 Comparison of Dossiers Developed for an Unapproved Product, Approved Product, and Unapproved Use of an Approved Product

	Unapproved Product Dossier	Approved Product Dossier	Unapproved Use Dossier
What is it?	A document containing factual presentations of evidence supporting the development of an unapproved product No characterizations/ conclusions should be made regarding the safety or effectiveness of the unapproved product	Comprehensive document containing clinical and economic evidence and information about an FDA-approved product, including unapproved use information supported by evidence Used to convey the overall value proposition of the product	A document containing factual presentations of evidence supporting the development of unapproved use(s) for which FDA approval is being sought for an FDA-approved product No characterizations/ conclusions should be made regarding the safety or effectiveness of the approved product for unapproved use(s)
How is it used?	Used per the manufacturer's discretion to communicate information to HCDMs before FDA approval of the product	Used by the manufacturer to respond to unsolicited requests from HCDMs after FDA approval of the product (dossier contains approved and unapproved use[s] information)	Used per the manufacturer's discretion to communicate information to HCDMs about unapproved use(s) for which FDA approval is being sought for an FDA-approved product
Can the product value proposition or value story be communicated?	Factual evidence grounded in clinical and economic evidence and information may be provided. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product	Value that is grounded in clinical and economic evidence and information should be described	Factual evidence grounded in clinical and economic information may be provided No characterizations or conclusions should be made regarding the safety or effectiveness of the approved product for unapproved use(s)
When should the manufacturer have the dossier ready for HCDMs?	At the manufacturer's discretion Typically, 6-12 months prior to anticipated FDA approval.	Any time after FDA approval of the product; at the discretion of the manufacturer Typically, soon after FDA approval and availability of the product approved label and price	Any time while the manufacturer is seeking FDA approval for unapproved use(s) of the approved product at the discretion of the manufacturer Typically, based on a key milestone at the manufacturer's discretion
Who from the manufacturer should communicate or provide the dossier?	Personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities		
What clinical content about the product should be in the dossier?	Factual presentation of clinical evidence for the unapproved product that is available at the time of communication No characterizations/ conclusions should be made regarding the safety or effectiveness of the unapproved product	Clinical evidence and information regarding an approved product, including any unapproved use(s) supported by evidence	Factual presentation of clinical evidence for unapproved use of an approved product that is available at the time of communication No characterizations/ conclusions should be made regarding the safety or effectiveness of the unapproved use
What economic content about the product should be in the dossier?	Anticipated product price (may be reflected as a range) The manufacturer has discretion on whether and how to provide economic information	Product price, health economics and outcomes research, economic models on budget impact and cost-effectiveness	Current product price or anticipated new product price or range if unapproved use(s) are approved The manufacturer has discretion on whether and how to provide economic information
When should the dossier be updated?	When new information becomes available and at the discretion of the manufacturer	When new information becomes available for approved or unapproved indications at the discretion of the manufacturer When new use(s) are approved	When new information becomes available at the discretion of the manufacturer

FDA = U.S. Food and Drug Administration; HCDM = health care decision-maker.

Health Care Decision-Maker

The term “health care decision-maker” (HCDM) is used throughout this document to refer to any health care personnel, committee, or organization that uses an evidence-based process for making health care coverage and reimbursement decisions for patient populations, including, but not limited to payers, health plans, integrated delivery systems, pharmacy benefit management companies, specialty pharmacies, health insurance companies, medical groups, hospitals, health systems, P&T Committees, HTA organizations, clinical practice guideline bodies, and other organized health care systems that make or influence population-based health care decisions.

Manufacturer

The term “manufacturer” is used throughout this document to refer to any company that develops, manufactures, or markets medical products, such as pharmaceuticals, DTx, diagnostic tests, or medical devices.

Product

The term “product” used throughout this document includes medical products such as pharmaceuticals, DTx, diagnostic tests, or medical devices. The AMCP Format was originally developed to address evidence for pharmaceutical products (drugs, biologics, and vaccines); however, today, the AMCP Format aims to also provide guidance for developing dossiers for nonpharmaceutical products, such as DTx, tests (e.g., companion diagnostic tests [CDTs]), and medical devices (e.g., syringes, glucometers, wearable technology) that may be relevant to formulary and medical policy decisions.

Approval

The term “approval” is used throughout this document as a general term to reflect the appropriate FDA regulatory decision-making process needed before the product may be commercialized. These decision-making processes may include FDA approval, clearance, licensures, etc.

Communication Between Manufacturers And HCDMs

The AMCP Format for Formulary Submissions Committee strongly recommends that manufacturer personnel with appropriate medical, scientific, or clinical training and credentials are the most appropriate to communicate,

provide, present, share, and discuss Unapproved Product Dossiers and Unapproved Use Dossiers and their contents with HCDMs. This recommendation is based on feedback by AMCP Format for Formulary Submissions Committee members and individual stakeholders representing payer organizations who have expressed the preference for appropriately trained and credentialed personnel with clinical or scientific degrees (e.g., PharmD, MD, PhD) and who possess medical, scientific, or health economics and outcomes research roles and responsibilities within the manufacturer to deliver clinical and economic evidence (e.g., not sales, marketing, or account managers). However, manufacturers may use their own discretion on this issue.

COMMUNICATION OF HEALTH CARE ECONOMIC INFORMATION FOR APPROVED PRODUCTS

Communication between HCDMs and manufacturers is strictly regulated by the FDA.¹¹ The FDA considers many types of proactive communication between manufacturers and HCDMs to be subject to promotional requirements. The Federal Food, Drug, and Cosmetic Act was amended in 1997, in part, to allow a different evidentiary standard for “health care economic information” (HCEI) provided to a limited audience of “formulary committees and similar entities.”¹² In 2016, the 21st Century Cures Act Section 3037 expanded and modernized Section 114 of the Food and Drug Administration Modernization Act (FDAMA), which related to communication of HCEI.¹³ The 2018 FDA Final Guidance clarifies common questions regarding manufacturers’ proactive communication of HCEI regarding drugs and devices to payers, formulary committees, or other similar entities.³ HCEI, as defined by FDAMA Section 114 and further clarified by the 21st Century Cures Act and the FDA Final Guidance, is subject to competent and reliable scientific evidence. The PIE Act was enacted as Section 3630 of the Consolidated Appropriations Act of 2023 and codified the FDA Final Guidance as part of FDAMA Section 114, effective January 1, 2023.⁴

COMMUNICATION OF APPROVED PRODUCT DOSSIERS

The FDA Final Guidance³ does not affect or change the manufacturer’s ability to develop and communicate Approved Product Dossiers that are provided to HCDMs upon an unsolicited request.

The unsolicited request process continues to be the mechanism through which the traditional Approved Product Dossiers are communicated and provided to HCDMs. This is largely because, for an Approved Product Dossier, the AMCP Format calls for information that may be inconsistent with a product’s FDA-approved labeling or does not otherwise meet substantiation requirements for promotional

communications. In December 2011, the FDA issued draft guidance entitled “Guidance for Industry: Responding to Unsolicited Requests for Off-label Information About Prescription Drugs and Medical Devices,” which outlines the FDA’s current thinking on the way manufacturers can respond to unsolicited requests for information about products.¹⁴ Manufacturers should follow this FDA guidance for the provision of an Approved Product Dossier in response to an unsolicited request. The request for information must be truly unsolicited. Specifically, the inquiry must be initiated by the requester (formulated in their own mind) without prompting, suggestion, or solicitation by the manufacturer or its employees. Manufacturers should place a statement on the Approved Product Dossier that it is being provided in response to an unsolicited request.

COMMUNICATION OF UNAPPROVED PRODUCT DOSSIERS AND UNAPPROVED USE DOSSIERS

HCDMs need and are interested in receiving information about unapproved products and unapproved uses of approved products for the purpose of early planning and budgeting for future coverage and reimbursement decisions before FDA approval.³ AMCP recommends that manufacturers provide HCDMs with Unapproved Product and Unapproved Use Dossiers 6 to 12 months before anticipated FDA approval or when information may be of most relevance to HCDM budget forecasting. Historically, it has been challenging for HCDMs to obtain, and manufacturers to communicate, such information when needed. To address this need, guidance on Unapproved Product Dossiers and Unapproved Use Dossiers were first included in Version 4.1 of the AMCP Format. HCDMs and manufacturers need to be cognizant that the availability of evidence and information at different points in a product’s life cycle varies. It is the manufacturer’s responsibility to include the most objective, relevant, and timely information in Unapproved Product Dossiers and Unapproved Use Dossiers when it becomes available. It is the HCDM’s responsibility to review the information and ask questions to gain a full understanding of a product’s profile.

ADDITIONAL CONSIDERATIONS FOR MANUFACTURERS

Given the complex regulatory and legal environment, manufacturers should consider and establish their own acceptable policies and procedures for developing and updating dossiers as well as communicating and disseminating dossiers, including the handling of requests. For example, consider policies and procedures to address the following inexhaustive list: (1) What specifically constitutes a request for a dossier versus a request for other medical

information; (2) How to fulfill requests for dossiers that have multiple indications or products for which a manufacturer has more than one dossier; (3) How to handle requests for future updates to dossiers; (4) When to develop Unapproved Product Dossiers and Unapproved Use Dossiers; and (5) How to communicate Unapproved Product Dossiers and Unapproved Use Dossiers.

BIDIRECTIONAL COMMUNICATION OF INFORMATION

Substantial ongoing and bidirectional communication and feedback between the HCDM and manufacturer is critical throughout the product evaluation process to manage expectations and maximize the quality of available evidence.

On one hand, HCDMs often view and criticize dossiers from manufacturers as lacking independence or objectivity. On the other hand, manufacturers invest significant time, resources, and costs in developing credible and evidence-based dossiers per the AMCP Format. Often, after a dossier is requested and received by the HCDM, the manufacturer is left with no feedback, comments, or conversation with the HCDM about the product information contained in the dossier.

To address the perception that dossiers lack independence or objectivity and in return for receiving a comprehensive dossier, HCDMs are encouraged to share with manufacturers concerns or questions about the evidence presented in the dossier, such as assumptions incorporated into economic models or completeness of clinical studies or substantiation of the proposed value proposition, to facilitate a productive dialogue. Feedback from HCDMs can help improve the quality of dossiers developed and provided by manufacturers. Feedback may include information on dossier completeness, objectiveness, relevance, usability, readability, and other user experiences with the document. Manufacturers and HCDMs should view bidirectional discussions about evidence and information in dossiers as a process to facilitate the HCDM’s understanding of the product evidence and information; educate the manufacturer on the HCDM’s evidentiary needs and perceived gaps; and improve the quality, content, and layout of the dossier. A shared vision to facilitate bidirectional communication between HCDMs and manufacturers is necessary to ensure and support appropriate evidence-based product evaluation.

It is important for HCDMs to communicate to manufacturers basic information such as product review timelines, the evaluation process, and any perceived evidence gaps that might exist. This allows the manufacturer an opportunity to respond with timely, relevant, and specific information that meets the needs of the HCDM. If the manufacturer is unable to provide certain information, it is better for the HCDM

to understand the limitations and reasons upfront. Early, ongoing dialogue between the HCDM and manufacturer is a critical success factor in optimizing the exchange of relevant, credible, and timely clinical and economic evidence for decision-making.

Dossiers timed for product launch may rely to a greater extent on modeled projections based on clinical trial evidence and assumptions related to market uptake. However, new evidence describing the actual use and effect of the product in a real-world setting should be developed to inform formulary, coverage, policy, and reimbursement decision-making across the product life cycle. Ongoing generation of real-world evidence serves the important purpose of further defining and validating claims related to product value. As such, ongoing and bidirectional communication between manufacturers and HCDMs can help inform that evidence.

To foster bidirectional communication, HCDMs should request and offer manufacturers the opportunity to meet and discuss the clinical and economic evidence in the dossier, and vice versa as both sides have legitimate business reasons for understanding each other's perspectives. HCDMs should welcome presentations from or discussions with appropriate manufacturer personnel (e.g., medical personnel, health economists) to address specific questions that they may have about the dossier or the product in question. HCDMs are encouraged to meet face-to-face with appropriate manufacturer personnel for scientific information exchange as well as commercial personnel responsible for market access and contracting discussions.

As stated earlier, one should view the dossier as a living document that may start out as an Unapproved Product Dossier, evolve as more evidence and information becomes available, and ultimately be updated and revised to become the Approved Product Dossier. HCDMs should provide feedback and insights to manufacturers on the emerging evidence throughout the development and life cycle of the product and related dossiers. Manufacturers may consider surveying HCDMs who have received the dossier for feedback regarding the content and quality of the dossier. HCDMs and manufacturers should consider and implement additional ways to increase communications between both stakeholders. This bidirectional communication process will help improve transparency and the quality of information sharing to support improved decision-making and optimize patient care.

Confidentiality

The confidentiality of evidence dossiers has been an area of concern since AMCP published the first version of

the AMCP Format in October 2000. Manufacturers have expressed concern that confidential information submitted as part of a dossier (e.g., unpublished studies, HCEI, economic modeling data) will become publicly available, thus exposing sensitive data to competitors. Concerns may be addressed with the execution of appropriate confidentiality agreements between the HCDM and the manufacturer. HCDMs should be aware that the ability of manufacturers to provide complete information is dependent on the recipient preserving the confidentiality of that information. We note that evidence dossiers submitted to government authorities in the United States (U.S.), the United Kingdom, and certain other countries are made available to the public; however, commercial-in-confidence information, when properly identified by the manufacturer, is redacted for the online version of the report. Special arrangements with public HCDMs, which require public disclosure of information received, may be necessary.

Manufacturers may require HCDMs to sign a confidentiality agreement before providing a dossier. Such agreements may also be required where prepublication data are shared. HCDMs should be willing to sign such agreements and adhere to their terms.

Product dossiers prepared in accordance with the evidence recommendations contained in the AMCP Format may contain HCEI and other information deemed proprietary by the company. Manufacturers should place a statement on the dossier when a confidentiality agreement is executed.

Updating Dossiers

UPDATING DOSSIERS FOR APPROVED PRODUCTS

A common question from manufacturers is, "When should a dossier be updated?" The AMCP Format for Formulary Submissions Committee recommends that dossiers be reviewed and updated when there are significant changes (e.g., changes to the prescribing information, line extensions, new safety information, or any information that materially affects the overall evidence). Ideally, dossier updates should be evidence-based (i.e., updates are triggered by availability of new evidence), for example:

- The manufacturer files a supplemental application to the FDA for a new indication; the regulatory decisions should be included in the dossier whether the new indication is approved or denied.
- The FDA issues advisory statements about the use of a product (e.g., establishes a new boxed warning).
- Significant new clinical or economic evidence becomes available, such as:

- New data to further support the use of the product for the approved indication.
- Identification of patients or subpopulations who may or may not benefit from receiving the product.
- Demonstration of real-world effectiveness and long-term effectiveness.
- Elucidation of long-term safety.

When updating a dossier, the manufacturer should conduct revisions to incorporate new evidence, delete obsolete information, and revise content and format to keep the dossier concise and relevant. The manufacturer may update the dossier by rewriting a new version of the dossier or amending the existing dossier with a supplemental document that acknowledges new evidence with proper citations, identifies obsolete information in the existing dossier, and describes any additional relevant information to the HCDM. The manufacturer should provide the HCDM with a way to identify newly added information (e.g., highlight revised/new sections or content, describe changes in an appendix, include a summary of changes in a cover letter).

When a manufacturer reviews a dossier for potential revision and determines that a revision is not necessary, this should be indicated on the title page of the dossier. In the absence of new evidence, dossiers should be evaluated for technical accuracy on an annual basis (e.g., changes in price, new model assumptions). All dossiers should include the original date of issue as well as the dates of any revisions or reviews for potential revisions.

When an HCDM requests a dossier that is under revision, the manufacturer may supply the current (last completed) version of the dossier, inform the requester of the status of the dossier and the expected time frame for completion of the revision, and offer to send the revised version when completed. Alternatively, the manufacturer may provide the updated version when completed.

Another common question from manufacturers is, “Can an updated dossier be provided to HCDMs who have previously requested and received a dossier?” In general, manufacturers should not freely and automatically send updated Approved Product Dossiers to previous requesters without an unsolicited request. However, HCDMs may, at the time of the original Approved Product Dossier request, include a statement that they would like to receive updated dossiers, if any, subsequent to the first dossier received. The request for updated dossiers must be for the same product as the original request, and the request must specify a specific length of time (e.g., for 6 or 12 months, or at the discretion of the manufacturer’s policies). While the AMCP Format does not specify a maximum length of time, the AMCP Format for Formulary Submissions Committee

recommends that the request for updated dossiers should not be indefinite and that manufacturers should determine their own policies and procedures. Allowance for this process will prevent HCDMs from having to submit numerous requests for updated information, especially since they may not be aware when updated dossiers may be available.

In addition, the explicitness of the unsolicited request for an updated Approved Product Dossier within a specific time frame will help manufacturers maintain compliance with the unsolicited request process. Whether to fulfill an unsolicited request for the dossier is at the discretion of the manufacturer. There may be rare instances where a manufacturer may decide to proactively send an updated Approved Product Dossier to an HCDM who had recently and previously received the dossier; for example, the dossier is being updated at the time of original request, there are significant errors in the previous version that was sent, or there are significant new patient safety warnings such as boxed warnings.

The manufacturer may decide that an Approved Product Dossier will no longer be kept current (e.g., the product is near the end of its branded lifespan or has lost exclusivity). If the manufacturer continues to provide the last version of an Approved Product Dossier to requesters, then the status (date created and/or date of last update) should be indicated on the dossier. If the manufacturer discontinues the availability of the Approved Product Dossier, then a rationale for its discontinuation should be provided to requesters of that dossier.

Following the initial FDA approval, a product may receive FDA approval for additional uses during its life cycle. Development and organization of the Approved Product Dossier for a product with multiple FDA-approved indications should be handled at the discretion of the manufacturer. For example, a manufacturer may develop separate sections for each indication within the same dossier or may develop separate dossiers for each indication or group of indications.

It is at the manufacturer’s discretion whether updates are required for any sections of the dossier to provide information that is concise, relevant, and objective.

UPDATING DOSSIERS FOR DIGITAL THERAPEUTICS

Updates to dossiers for DTx are recommended when changes directly affect the effectiveness or safety of the product or how patient care is delivered, such as changes to a care algorithm or changes in patient usability that may impact effectiveness or safety. Updates that impact how patient data will be stored, shared, or utilized do not typically require an update to a digital therapeutic dossier. However, communication with HCDMs may be warranted.

In general, digital therapeutic dossiers do not need to be updated when there are minor updates or changes to the product that do not impact patient care or the effectiveness or safety of the product.

UPDATING DOSSIERS FOR UNAPPROVED PRODUCTS AND UNAPPROVED USES

Manufacturers may use discretion on when to develop and how often to update Unapproved Product Dossiers and Unapproved Use Dossiers to ensure their usefulness to HCDMs. Certain time points or milestones may be considered for triggering the update of an Unapproved Product or an Unapproved Use Dossier, such as initiation or completion of a phase 3 trial or application/submission for FDA approval. AMCP and the AMCP Format for Formulary Submissions Committee do not intend to prescribe specific time points or frequency of updates.

Dossier Page Limits

The AMCP Format provides guidance regarding page limit recommendations for individual sections of a dossier. These recommendations are for general guidance only, as there are many factors that may influence the appropriate section length for a product. Manufacturers should present relevant evidence and product information as concisely and clearly as possible to streamline the evidence acquisition and review process. Manufacturers should not include overly verbose or superfluous content to meet page recommendations.

Special Content Considerations

Biosimilars

A biosimilar is defined as a biological product that “is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”¹⁵ According to the FDA, for a product to be a biosimilar or interchangeable, the manufacturer must submit a 351(k) biologics license application (BLA) that demonstrates biosimilarity.¹⁵

The FDA has provided guidance on the analyses and testing that are required to demonstrate biosimilarity and

Submission Of Dossiers

Manufacturers should submit dossiers in an electronic format rather than in print. Electronic formats may include email, online platforms (e.g., Formulary Decisions, manufacturer websites), or other electronic technologies. This will help reduce resource expenditures and improve health care system staff’s ability to transfer evidence directly into P&T Committee submission monographs. This includes any economic models provided in the dossier, which should be presented electronically (e.g., Microsoft Excel workbook or an alternative electronic format that is agreed upon by the requesting organization and the manufacturer) to facilitate ongoing dialogue as well as allow flexibility for user-defined analyses.

Pre-Approval Information Exchange

PIE is used by manufacturers and HCDMs to facilitate the exchange of product-specific information that may be relevant to HCDM budgets and formulary decision-making. PIE communications are typically initiated by manufacturers and are generally created in tandem with Unapproved Product Dossiers or Unapproved Use Dossiers. PIE should generally include information from ongoing and completed trials, important timeline information, and information relevant to patient access. AMCP encourages manufacturers to proactively engage with HCDMs in a timely fashion to support critical planning processes, and manufacturers should continue to update HCDMs as new information becomes available.

interchangeability.¹⁶ Companies that develop biosimilars should incorporate these considerations into dossiers to allow HCDMs to fully evaluate these products.

Because biosimilar products, as well as multiple indications for a biosimilar product, may gain FDA approval based on evidence that was generated for the reference biologic, biosimilar companies must clearly document whether clinical trials and other studies (e.g., pharmacokinetic studies) were conducted with the reference biologic or the biosimilar product. HCDMs should be able to distinguish whether biosimilars are supported by direct or extrapolated evidence.

Additional information on FDA guidance related to biosimilars may be found in the following:

- Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry. May 2019.¹⁶
- Biologics Price Competition and Innovation Act of 2009 (BPCI Act).¹⁷
- Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. April 2015.¹⁸
- Guidance for Industry: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry. April 2019.¹⁹
- Nonproprietary Naming of Biological Products: Update Guidance for Industry. March 2019.²⁰
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the Public Health Service Act. Draft Guidance. August 2014.²¹
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Draft Guidance. December 2016.²²
- Questions and Answers on Biosimilar Development and the BPCI Act. December 2018.¹⁵
- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (revision 2). December 2018.²³

Companion Diagnostic Tests

CDTs have been defined in various ways and have been referred to as pharmacogenomics, pharmacogenetics, targeted therapy, personalized medicine, precision medicine, biomarker testing, etc. The FDA definition describes a CDT, or an in vitro companion diagnostic device, as one that provides information that is essential for the safe and effective use of a corresponding therapeutic product.²⁴

More specifically, in the AMCP Format, a CDT is defined as a laboratory test or assay that provides predictive and differential information about a patient's response or anticipated response to drug therapy. This contrasts with diagnostic or prognostic tests, which provide information about the disease process rather than response to treatment. The Companion test Assessment Tool (CAT) was developed to assist HCDMs in determining whether a full technology review is necessary and, if so, what factors are likely to be most influential in the CDT's overall value.²⁵

There are multiple sources for background information regarding CDTs. In addition, various other analyses evaluating frameworks and cost-effectiveness are available.²⁶⁻³¹

DOSSIERS FROM PHARMACEUTICAL MANUFACTURERS VERSUS CDT MANUFACTURERS

Implementation of dossier requests for CDTs using the AMCP Format may be complicated by the variety of potential relationships between a pharmaceutical manufacturer and CDT manufacturer/developer.

The following are possible CDT development scenarios, in no preferential order:

- CDT co-developed with the pharmaceutical and FDA-approved together with the pharmaceutical.
- CDT developed independently of the pharmaceutical, typically after approval of the pharmaceutical.
- CDT developed independently and targeted for a class of medications.

In each of these scenarios, the pharmaceutical manufacturer may or may not be the same as the CDT manufacturer/developer. In the case where the pharmaceutical manufacturer is different from the CDT manufacturer/developer, the two companies may or may not have business agreements to work collaboratively in the development and marketing of the drug and CDT. Obtaining evidence for CDTs may also be complicated when a clinical laboratory test is not reviewed, cleared, or approved by the FDA (a laboratory developed test when testing is a service and not a product or kit). Thus, depending on the development pathway, manufacturers and CDT developers may have different responsibilities and processes regarding evidence submission to HCDMs.

Given the potential complexity of regulatory processes, data sources, and manufacturer relationships, the AMCP Format includes the following recommendations for developing dossiers with CDT evidence:

- The CDT is co-developed with a pharmaceutical.
 - The manufacturer should provide CDT evidence as part of the pharmaceutical dossier in the AMCP Format because the evidence for the safety, efficacy, and value of the pharmaceutical is inherently linked to the CDT.
- The CDT is developed independently of the pharmaceutical.
 - If the CDT is required in the drug label, the manufacturer should, if possible, provide data on the clinical validity, clinical utility, and economic value of both the pharmaceutical and CDT in the drug dossier. Information on analytic validity should be provided if feasible.
 - If the CDT is not required in the pharmaceutical label, then the CDT developer should provide a "CDT dossier" that provides information as outlined in this section.

- The CDT is developed independently and is targeted for a class of medications.
 - The CDT developer should provide a “CDT dossier” that provides information as outlined in this section.

Comparative Effectiveness Research

While the AMCP Format does not require manufacturers to use any particular research design to present evidence of benefit, safety, cost-effectiveness, or financial impact of their products, it does strongly recommend that manufacturers include evidence from comparative effectiveness research (CER) studies as they become available.

Initial approval of products by the FDA is based on randomized controlled trials (RCTs) comparing the product to placebo or, more preferably, a relevant active comparator. Because of their highly controlled research settings, RCTs are considered the gold standard for clinical research with high internal validity.

Real-world data from CER is usually not available at the time of new product launch. However, in subsequent years, real-world CER may be conducted by manufacturers as well as by other researchers, and the new evidence should be incorporated into the dossiers. RCTs and CER can complement each other by generating evidence to answer questions that may be more appropriate in one study design or the other. For example, sometimes, it is not ethical or feasible to conduct RCTs.

There are many study designs that may be used to conduct CER. The AMCP Format does not dictate the process by which evidence is developed, nor does it provide methodological guidance. The reader is referred to other sources for more background information on various study designs such as Bayesian and adaptive trials,^{32,33} pragmatic clinical trials,^{34,35} prospective observational studies,³⁶ retrospective observational studies,³⁷ systematic evidence reviews including indirect treatment comparisons and network meta-analyses,³⁸⁻⁴¹ and modeling studies.⁴²

For assessing evidence from CER studies, various tools may be used to evaluate different types of outcomes research,⁴³ including prospective and retrospective observational studies,⁴⁴ modeling studies,⁴⁵ and indirect treatment comparison studies.⁴⁶ HCDMs may also use tools to assess the body of evidence, such as Institute for Clinical and Economic Review (ICER) Evidence Rating Matrix,⁴⁷⁻⁴⁹ Grading of Recommendations Assessment, Development and Evaluation (GRADE),⁵⁰⁻⁵² and refer to good practices recommended by The Professional Society for Health Economics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE).⁵³

Digital Therapeutics

AMCP defines DTx as products—including software, applications (i.e., apps), or programs—designed to stand alone or work in combination with existing medications or treatments to help patients prevent, treat, and/or manage their diseases, while ensuring optimal health outcomes from therapy. A key distinguishing feature of a DTx product, either prescription or nonprescription, is that it makes a health claim that is validated by a third party (e.g., a regulatory authority). However, definitions of digital health, DTx, and digital health technology (DHT) differ across various sources and are generally broad, encompassing many types of products (see Table 2). DTx are generally considered a subset or subcategory of DHT, which includes the full spectrum of digital technologies (i.e., health system tools, clinician-facing tools, and patient-facing wellness; care support; and monitoring, diagnostic, and therapeutic products).

The role of the AMCP Format with DTx 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 volume of DTx products coming to the market, standardized resources will be critical in allowing HCDMs 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 for the following:

- Functionality
- How DTx are made available (e.g., 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 (i.e., is the product intended to be used with certain drugs or classes of drugs? Or could it be used as a stand-alone product?)
- Available versions (e.g., 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. The 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

TABLE 2 Definitions Related to Digital Therapeutics

Term	Organization	Definition	Categories
DTx	AMCP	Products (software, apps, or programs) designed to stand alone or work in combination with existing medications or treatments to help patients prevent, treat, and/or manage their diseases 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).	Treat a disease Manage a disease Improve a health function (e.g., prevent a disease)
	DTA	Health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health. ⁵⁴	
Digital health	FDA	Technologies that use computing platforms, connectivity, software, and sensors for health care and related uses.	Mobile health Health information technology Wearable devices Telehealth/telemedicine Personalized medicine
DHT	NICE	Apps, programs, and software used in the health and social care system. They may stand alone or be combined with other products, such as medical devices or diagnostic tests.	Provide an intervention Aid understanding/communicating Offer system services
	DTA	The term DHT represents the full spectrum of digital health products that are available to patients, caregivers, clinicians, and health systems. DHT product spectrum includes various medical device categorization sub-classifications (e.g., health software and digital medical device), in addition to various product indication types (e.g., health system tools, clinician-facing tools, and patient-facing wellness; care support; and monitoring, diagnostic, and therapeutic products).	

Adapted from AMCP Partnership Forum Proceedings: The evolving role of digital therapeutics. *J Manag Care Spec Pharm.* 2022;28(7):804-10. Available at: <https://doi.org/10.18553/jmcp.2022.22093>. Accessed December 30, 2023.

AMCP = Academy of Managed Care Pharmacy; DHT = digital health technology; DTA = Digital Therapeutics Alliance; DTx = digital therapeutics; FDA = U.S. Food and Drug Administration; NICE = National Institute for Health and Care Excellence.

sections within Section 3.0B Clinical Evidence. Other types of evidence and studies that do not fit within Section 3.0B, such as preference testing, usability testing, and information on the validation of the endpoints/scales may be included in Section 5.0B Additional Supporting Evidence. The dossier must clearly specify which version of the DTx product it addresses.

HCDMs require meaningful evidence of efficacy, including clinical trials and real-world evidence, to support evaluation and coverage. Although the body of evidence for a DTx product may vary based on product type, claim, and approval pathway, the dossier should include the

highest quality data available (i.e., data demonstrating an improvement compared to standard of care with rigorous methodology). The evidence section should be updated to reflect the current product version.

In addition, a Table of Highlights for Digital Therapeutics should be included in the product information section of the dossier (see Sections 2.1.1A, 2.1.1B, and 2.1.1C). There is also a required Privacy Data and Security appendix and optional appendices for engagement and screenshots (Sections 6.4A, 6.6B, and 6.6C). See Table 3 for FDA performance indicators on privacy and security.

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

- *DTx as a stand-alone therapy.* If the DTx product is a software-only intervention independent of other pharmaceutical products or the DTx product is intended to be an add-on therapy to other standard of care treatments, a stand-alone dossier should be developed.
- *DTx used with other therapies.* If the DTx product is intended to be used with certain classes of medications (e.g., insulin or inhaled medications for asthma), a

stand-alone dossier should be developed.

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

TABLE 3 Nine FDA Key Performance Indicators on Privacy and Security, as Recommended by the AMCP Digital Therapeutics Advisory Group⁵⁵⁻⁵⁸

Indicator	Description
Complaints	Information on the process used to track complaints, concerns, and questions from users and other sources to help the organization identify defects and improve performance.
Cybersecurity	Processes for how an organization maintains data security by providing safeguards to ensure the delivery of critical services, detect a cybersecurity event, respond to an event, and restore any capabilities or services that were impaired due to a cybersecurity incident.
Data quality	Methods an organization uses to verify the effectiveness of its data retention and integrity measures (including backups and use of encryption) to ensure that critical data is restricted to authorized users and not altered in an unauthorized manner by destructive malware, ransomware, malicious insider activity, or through inadvertent mistakes.
Defects	Identify software defects that may cause the product to behave differently from the intended behavior or lead to false-positive or false-negative results.
Device activation/user adherence	Define the interactions between the user and the device on a rolling basis to ensure device adherence and adequate user training that allows for effective use of the device.
Regression testing	Process for testing when the medical device company makes an update or code modification to the software.
Releases	Effective software releases and updates are fundamental not just to deploy services to users but also to resolve emergency, safety, critical, and security events. Medical device companies should outline deployment strategies with active control mechanisms to push releases and updates securely and effectively.
Rollbacks	Process for restoring the software product to an earlier version when a recently released version encounters issues.
Services	Process for how the developer provides software and support services to ensure that the product is delivered appropriately and on time.

Dossiers For Clinical Laboratory Tests and Medical Devices

The AMCP Format may be used to convey evidentiary needs for medical devices. Because of the vast number, type, and complexities of medical devices, it is recommended that medical devices that are directly related to the use of a drug are most relevant and applicable for the AMCP Format. Examples of medical devices where the AMCP Format may apply, include but are not limited to, implantable drug delivery devices, blood glucose measuring devices, test strips (e.g., blood, urine), inhalation devices (e.g., nebulizers), and health assessment devices and tests that elucidate health status, diagnosis, or prognosis. Medical device companies

are encouraged to develop and make available medical device dossiers for HCDMs.

If a medical device company chooses to use the AMCP Format to create a device dossier, the company may indicate “not applicable” for AMCP Format sections that do not apply to devices.

In August 2017, the FDA released final guidance, “Use of Real-world Evidence to Support Regulatory Decision-making for Medical Devices,” for purposes of FDA approval or clearance of medical devices. The information in the final guidance might be instructive in providing examples of real-world evidence and data that the FDA considers appropriate for regulatory approval or clearance of medical devices.⁵⁹

Heterogeneity of Treatment Effect

Heterogeneity of treatment effect is defined as “nonrandom explainable variability in the direction and magnitude of individual treatment effects, including both beneficial and adverse effects.”⁶⁰ Response to a treatment, whether beneficial or adverse, varies from individual to individual. It is important for HCDMs to understand heterogeneity of treatment effect when evaluating therapies for clinical, coverage, and reimbursement decisions for patients. While evaluating the body of evidence for a treatment, HCDMs

need to consider variability between individual patients, within populations studied, and between clinical studies. Factors known to be associated with disparate treatment outcomes should be described. Identification of heterogeneity should be noted in Section 2.2.2B(3), and the evidence and studies to support it should be summarized in Section 3.0B or Section 5.0B, as appropriate. Readers are referred to additional information on heterogeneity of treatment effect.⁶¹⁻⁶⁴

Evidence Recommendations for Unapproved Product Dossiers

SECTION 1.0A – HIGHLIGHTS AND OVERVIEW

SECTION 2.0A – PRODUCT INFORMATION AND DISEASE DESCRIPTION

SECTION 3.0A – CLINICAL EVIDENCE

SECTION 4.0A – ECONOMIC INFORMATION

SECTION 5.0A – ADDITIONAL SUPPORTING EVIDENCE

SECTION 6.0A – DOSSIER APPENDICES

1.0A Highlights and Overview

The recommended length of Section 1.0A is two pages (maximum four).

This section provides an at-a-glance overview of the key information about an unapproved product.

Consistent with the FDA “Guidance on Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices,” manufacturers should not make claims, characterizations, or conclusions regarding the safety, effectiveness, or uses of the unapproved product. Manufacturers should provide factual and

objective information about the unapproved product in an Unapproved Product Dossier.¹⁴

There is no Executive Summary in an Unapproved Product Dossier, as there is in an Approved Product Dossier, because the intent of an Executive Summary is to convey the overall value proposition of a product based on clinical and economic evidence. In an Unapproved Product Dossier, no characterization or conclusions should be made regarding the safety or effectiveness of an unapproved product. However, key information should be included about the unapproved product, using the Table of Highlights for Unapproved Products in Table 1.1A.

It is important to acknowledge that information may or may not be available depending on the phase of the product development and life cycle (e.g., phase 2 vs. phase 3). If information is not yet available or cannot be disclosed per the manufacturer’s discretion, indicate “N/A.” As information becomes available for communication, the manufacturer should update the dossier.

Be brief and concise. Provide citations and references to indicate the source of information where applicable.

TABLE 1.1A

TABLE OF HIGHLIGHTS FOR UNAPPROVED PRODUCTS

Type of Information	Description of Information
Revision dates	List the dates of revisions to this table in reverse chronological order
Manufacturer name	List the names of companies involved in developing and marketing the unapproved product
Unapproved product name	List the names of the unapproved product (brand, generic, chemical, molecular, company-assigned name, research compound number)
Drug class	Describe the drug class in which the product belongs
Disease or anticipated indication	List the diseases, indications, and target populations for which the unapproved product is being studied and FDA approval is being sought

Type of Information	Description of Information
Special FDA designations	List special designations per FDA (e.g., fast track, orphan, breakthrough) and the date of designation; provide links to source information (e.g., FDA, press release)
FDA submission date	List the date of NDA/BLA submission to the FDA
FDA Advisory Committee meeting	List the date of the planned or anticipated FDA Advisory Committee meeting or indicate if FDA has determined one is unnecessary
Anticipated FDA approval date	List the date or time frame (e.g., year, quarter) of anticipated FDA approval
Product launch date	List the date of anticipated product launch in the market
Approval dates in other countries (outside of the U.S.)	List other countries and (anticipated) approval dates
Phase 3 trials completed	List the name or citation of trials and dates completed, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Phase 3 trials in progress	List the name or citation of trials and dates in progress, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Phase 2 trials completed	List the name or citation of trials and dates completed, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Phase 2 trials in progress	List the name or citation of trials and dates in progress, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Anticipated routes and dosing information	Describe the routes of administration for the unapproved product that were used in clinical trials and anticipated to be approved by the FDA
Anticipated location/settings for product administration	Describe the location or health care setting where the product was administered in clinical trials and anticipated to be given when approved by the FDA. Mention whether health care professionals/location require specific certifications to administer the product
Prevalence of condition associated with anticipated indication in the U.S.	Express results per 100,000 (e.g., 1 per 100,000 women, 5 per 100,000 live births, 10 per 100,000 per year)
Annual incidence of condition associated with anticipated indication in the U.S.	Express results per 100,000 (e.g., 1 per 100,000 women, 5 per 100,000 live births, 10 per 100,000 per year)
Product pricing information	Indicate the anticipated annual cost per patient of the product in terms of price ranges or corridors rather than an absolute dollar figure. For example, indicate one of the following: <input type="checkbox"/> ≥\$1,000,000 <input type="checkbox"/> \$500,000 to \$999,999 <input type="checkbox"/> \$300,000 to \$499,999 <input type="checkbox"/> \$100,000 to \$299,999 <input type="checkbox"/> \$50,000 to \$99,999 <input type="checkbox"/> \$10,000 to \$49,999 <input type="checkbox"/> ≤\$9,999 Alternatively, or in addition, indicate any other information that might help HCDMs consider the anticipated cost impact of the unapproved product
Anticipated patient support programs	Describe potential plans for patient support programs
Anticipated distribution strategy	Describe anticipated distribution plans for product (e.g., limited distribution)

BLA = biologics license application; FDA = U.S. Food and Drug Administration; HCDM = health care decision-maker; NDA = new drug application; U.S. = United States.

2.0A Product Information and Disease Description

2.1A PRODUCT INFORMATION

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

Manufacturers are encouraged to provide as much detailed, factual, and objective information about the unapproved product as possible, without making claims, characterizations, or conclusions regarding safety and effectiveness. It is important to acknowledge that information may or may not be available depending on the phase of the product development and life cycle (e.g., phase 2 vs. phase 3). If information is not yet available or cannot be disclosed per the manufacturer's discretion, indicate "N/A." As information becomes available for communication, the manufacturer should update the dossier regularly and revise the corresponding information in Section 1.0A Highlights and Overview.

The following are the components that may be included (per FDA Final Guidance,³ the PIE Act,⁴ and AMCP Format recommendation):

1. A clear statement that the unapproved product is not FDA approved and that the safety or effectiveness of the unapproved product has not been established.
2. Information related to the phase of product development (e.g., the status of any studies in which a product is being investigated and how it relates to the overall product development plan, whether a marketing application for the product has been submitted to the FDA,

or when such a submission is planned).

3. Product information (e.g., drug class, device description, features).
 - Generic, brand, chemical, or other given name of the unapproved product.
 - Proposed mechanism of action.
 - Pharmacology, pharmacokinetic, and pharmacodynamic information.
 - Drug/drug, drug/food, and drug/disease interactions.
 - Dosing and administration information (usually from clinical trials).
 - Anticipated access and distribution information.
4. Information about the indications being sought, such as information from the clinical study protocols about endpoints being studied and the patient population under investigation (e.g., number of participants enrolled, subject enrollment criteria, subject demographics).
5. Product pricing information.
6. Anticipated patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).
7. Anticipated product-related programs or services (e.g., patient support programs).
8. Information regarding FDA expedited approval, priority review, breakthrough therapy, accelerated approval or fast track designation.
9. Other factual information per the manufacturer's discretion

For DTx products, complete the Table of Highlights for Unapproved Products (see Table 1.1A) in addition to the Table of Highlights for Digital Therapeutics (Table 2.1.1A).

TABLE 2.1.1A

TABLE OF HIGHLIGHTS FOR DIGITAL THERAPEUTICS

Type of Information	Description of Information
Product version	<ul style="list-style-type: none"> • Include version of application that the dossier applies to
Approval pathway	<ul style="list-style-type: none"> • 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) • Health care setting • Institutional setting (nursing home, long-term care)
Relationship to other therapies	<ul style="list-style-type: none"> • Stand alone • Add-on therapy to standard of care • Replaces existing therapy • Co-prescribed with pharmacologic therapy
Language	<ul style="list-style-type: none"> • Languages in which the product is available
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 nonprescription DTx product (in-person or virtual engagement) Direct authorization by an employer for a nonprescription DTx product Direct authorization by a payer for a nonprescription DTx product “Authorized clinical protocol” established by an 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)
Components required for the software to deliver its therapeutic value	<ul style="list-style-type: none"> Additional hardware or software required
Host technology and required hardware components (if applicable)	<ul style="list-style-type: none"> 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 (e.g., Chrome, Edge, Safari) Operating system (e.g., iOS, Android)
Technical assistance availability	<ul style="list-style-type: none"> In-app support via chat or call center availability

DTx = digital therapeutics; FDA = U.S. Food and Drug Administration; HCDM = health care decision-maker; iOS = Apple operating system; PC/Mac = refers to computers running IBM-based operating systems/computers produced by Apple.

2.2A DISEASE DESCRIPTION

The disease description should be a top-line overview focusing on the specific patient populations for which the product is 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 the population of U.S. patients. Present a summary of information from the literature for topics, including, but not limited to the following:

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, ethnicity, gender, income, or geographic region.
6. Unmet needs of current therapies.

This section may be expanded to provide greater detail for unapproved products that would 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 unapproved products that are seeking FDA approval to treat rare diseases for which relatively little information may be available in the public domain. Likewise, expanded information is useful for unapproved products that could be costly, have few competing or generic alternatives, or have limited distribution or access points.

3.0A Clinical Evidence

Section 3.0A should consist of studies that support the proposed use and clinical benefits of the product in a clear and concise format.

It is important that Section 3.0A be transparent and reflect the full body of clinical evidence that exists for an unapproved product. AMCP acknowledges that available evidence for an unapproved product may be limited to a few studies, and inclusion of all studies in the dossier is sensible. 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 the evidence be separated into the following categories:

1. An overview of clinical information should be provided on the first page of Section 3.0A.

2. Pivotal data, and in some instances other RCTs and/or real-world evidence, that contribute significantly to the knowledge base of the unapproved product should be included as *study summaries* (see Section 3.1A) and *evidence tables* (see Section 3.2A).
3. Informative but smaller and/or less rigorous studies that may add to the evidence base should be included as *evidence tables* (see Section 3.2A) 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 Section 3.0A should define a specific set of objective criteria for inclusion and exclusion of studies and describe how studies were selected for inclusion and exclusion. 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 on ClinicalTrials.gov. These characteristics include, but are not limited to, study design, number of participants, 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. Because these definitions may vary depending on the context of the unapproved product, clinical setting, incidence/prevalence of the disorder, and available treatment alternatives, 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 participants represent the target population, as described in Section 2.2A, 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 limitations that erode generalizability should be disclosed.

Considerations for Section 3.0A:

- 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 a 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 Section 3.0A. 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 unapproved product may be appropriate, and other clinically related outcomes.

- 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 peer-reviewed published medical journals are preferred. When peer-reviewed 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.
- If the results of a trial have been reported in more than one journal article or conference abstract, poster, or scientific podium 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 participants. Discuss important study findings and comment on their implications for different patient populations.
- Data summarized in Section 3.0A should not be re-summarized in Sections 2.0A and 5.0A.

3.1A STUDY SUMMARIES

The recommended length of each study summary is two pages (maximum five).

Study summaries should include the following items where available and applicable:

1. Publication citations, study name, ClinicalTrials.gov ID number, and funding source.
2. Objective, location, and study start and completion dates.
3. Trial design, randomization, and blinding procedures.
4. Setting, inclusion, and exclusion criteria.
5. Baseline patient characteristics and demographics.
6. Drop-out rates and procedures for handling drop-outs (e.g., intention-to-treat [ITT], per protocol).
7. Treatments, interventions, dosage regimens, washout period, concomitant therapies, etc.
8. Clinical outcomes evaluated, measured, and collected, delineating primary versus secondary endpoints, as well as pre-specified versus post hoc

analyses. When applicable, information on surrogate endpoints should also be provided (i.e., for expedited pathways).

9. Measures of effect (e.g., risk difference, risk ratio, odds ratio, number needed to treat), statistical significance of outcomes, and power calculations.
10. Validation of outcomes instruments, if applicable.
11. Generalizability of the population treated.
12. Study limitations, as stated by the authors.

3.2A EVIDENCE TABLES

The recommended length of a row in the evidence table is less than one page (maximum two) for each study.

Evidence tables should include the following data elements:

- Citation (if unpublished, give abstract information or indicate “data on file”)
- Treatments
- Sample size and length of follow-up
- Inclusion and exclusion criteria
- Design
- Primary endpoints
- Secondary endpoints
- Results (provide an explicit statement of effect size, and/or absolute risk difference, not just relative risk reduction and statistical significance. Within the Results column, include a table of key results.)
- Statistical significance (e.g., p-value and confidence interval)

It may be helpful to display evidence tables in landscape rather than portrait formats with appropriate use of abbreviations and other acceptable ways to display data in a clear, objective, and concise way.

4.0A Economic Information

AMCP acknowledges that the price of an unapproved product is typically not disclosed until final approval by the FDA or market launch of the product. The FDA recognizes that HCDMs need and are interested in receiving information from manufacturers about unapproved products. HCDMs need such information to begin to inform their plans and budgets for future coverage and reimbursement decisions well before FDA approval. A key piece of information is product pricing.

AMCP strongly recommends that manufacturers provide as much product pricing information as possible so that HCDMs may plan and budget for future coverage and reimbursement decisions prior to FDA approval.

Product pricing information may help HCDMs consider the potential economic impact and consequences of the

product. Product pricing information may be provided in the form of price ranges or corridors, rather than a specific dollar figure.

Budget impact and cost-effectiveness models may not be feasible to construct or communicate prior to FDA approval because such models rely on certain outcomes and assumptions regarding effectiveness and safety of a product and target population or indication. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product.

When deemed necessary, manufacturers may request execution of nondisclosure agreements so that sensitive or confidential pricing information may be shared or discussed in a protected manner.

Economic information about an unapproved product may be provided in a variety of ways, which may include the following:

- Estimated cost or range of cost (e.g., per year, per patient, per course)
- Directional estimations of cost or range of cost relative to other treatment options
- Rationale for pricing strategy

5.0A Additional Supporting Evidence

Only in limited circumstances would this section be populated, such as evidence from use outside of the U.S. When available, relevant data supporting the unapproved product (from clinical practice guidelines, HTAs and systematic reviews, modeling, and pharmacoeconomic and pharmacoequity studies) should be included. These data would often consist of ex-U.S. sources so applicability to U.S. markets should be considered.

5.1A 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 unapproved 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 unapproved product, its comparators, and the disease state and how the unapproved 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.

5.2A 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) and the Patient-Centered Outcomes Research Institute (PCORI), reports from the 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 unapproved product.

5.3A OTHER ECONOMIC OR OUTCOMES EVIDENCE

Include published studies that result in economic evidence or other outcomes that do not fit in Section 3.0A, for example, pharmacoeconomic, modeling, health care utilization, pharmacoequity considerations, and productivity studies, including 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.

5.4A EFFECT ON EQUITY

Phase 3 RCTs and cost-effectiveness analyses typically do not address barriers to the equitable use of a product. Such barriers may include, but are not limited to, access to specialists, health disparities and social barriers, stigma, and the patient's ability to afford and utilize a medication. While health equity data for new interventions may initially be limited, equity considerations often have implications for value assessment and should be discussed.

5.5A EFFECT ON QUALITY MEASURES

This section is to accommodate information and research where the unapproved 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, this section is not applicable.

5.6A 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' families and caregivers. If no information exists, this section is not applicable.

6.0A Dossier Appendices

The following information is valuable to HCDMs and should be included in Section 6.0A, when possible.

6.1A REFERENCES CONTAINED IN DOSSIERS

Include citations for all known published clinical and economic studies in the bibliography section. Reprints of relevant published studies should be available on request, and where possible, links should be provided to original sources if they are free.

6.2A ECONOMIC MODELS

Include basic economic models that incorporate anticipated population and utilization projections, where possible.

6.3A MATERIAL SAFETY DATA SHEET

Include or link to a Material Safety Data Sheet for the product.

6.4A APPENDICES SPECIFIC TO DTX PRODUCTS

Privacy and data security

Information related to privacy and security is required to be included in an AMCP dossier. Although the intended audience of the dossier is HCDMs who may lack the expertise needed to thoroughly evaluate the privacy and data security specifications for DTx products, a thorough evaluation of privacy and data security is required since this is essential to a comprehensive evaluation. Moreover, a review of privacy and safety may be performed prior to an evaluation of the clinical evidence by a P&T committee or body. If needed, HCDMs may seek additional expertise from data information technology/security experts, establish a DTx subcommittee, or have a separate group, such as an innovation center, assist with DTx evaluation. DTx manufacturers may work directly with HCDMs to integrate and implement DTx. Manufacturers may also provide relevant links to related information (i.e., privacy policies, terms of service).

Items to be addressed in a privacy and data security appendix include the following:

- Certifications (e.g., SOC 2, HITRUST, PCI DSS, ITIL, ISO 27001, CIPP)
- Data encryption: software supports SSL encryption
- Antivirus software

- Data protection security measures
- Security information and event management solutions (SIEM), web application firewalls (WAF), SECOPS monitoring, managed security providers (MSSPs), security orchestration automation and response platforms (SOAR)
- Data backup and recovery solutions
- Details on where data are stored
- Processes for secure disposal of information technology equipment and media
- Intrusion detection systems (IDS) or intrusion prevention systems (IPS) used.
- Parental restrictions for minors
- Data integrity
- Cybersecurity
- Data privacy processes
- Multifactor authentication
- Ransomware protection
- Other hack prevention methods

Engagement

Manufacturers may specify how they define engagement in an optional appendix. Due to the wide variety of DTx products 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 DTx products. If engagement measures were used in clinical trials or real-world evidence, they may be addressed in Section 3.0A or Section 5.0A.

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 health care professionals may also be included.

Evidence Recommendations for Approved Product Dossiers

SECTION 1.0B – EXECUTIVE SUMMARY

SECTION 2.0B – PRODUCT INFORMATION AND DISEASE DESCRIPTION

SECTION 3.0B – CLINICAL EVIDENCE

SECTION 4.0B – VALUE AND MODELING REPORT

SECTION 5.0B – ADDITIONAL SUPPORTING EVIDENCE

SECTION 6.0B – DOSSIER APPENDICES

1.0B Executive Summary: Clinical and Economic Value of the Approved Product

The recommended length of Section 1.0B is five pages (maximum eight).

This section of the submission represents the principal opportunity for a manufacturer to briefly summarize the value of its product. The Executive Summary should highlight the key evidence on clinical and economic value and be representative of the body of evidence found in Sections 2.0B through 5.0B. The manufacturer should briefly describe the clinical and economic information presented in the dossier using the layout described in

Sections 1.1B and 1.2B and state the expected per unit product cost. Based on this information, the manufacturer should articulate a value argument to justify these expected expenditures in the context of the clinical evidence and anticipated effects on health and economic outcomes. Throughout the Executive Summary, the reader should be referred to those places in the full dossier that justify claims and other statements made in the Executive Summary. Hyperlinks to these areas are especially helpful. If appropriate, additional context should be provided to emphasize the potential value or unmet need of the disease and relevant aspects of the therapeutic landscape (e.g., is the endpoint or population representative or meaningful outside of a clinical trial? Are study methodologies suitable for the type of study? Are assumptions for cost-effectiveness analyses relevant/valid?)

1.1B CLINICAL BENEFITS

Begin with the indication approved by the FDA for the product and a short synopsis of the efficacy and safety information from the prescribing information and clinical trials. Summarize the clinical benefits of the proposed product, in terms of the following:

1. Efficacy and effectiveness.
2. Comparative effectiveness relative to available alternative therapies.

3. Safety/tolerability.
4. Shortcomings of previously available treatment and the unmet medical need that the proposed therapy addresses.

1.2B ECONOMIC BENEFITS

Summarize the economic benefits of the proposed product, in terms of the following:

1. Cost per unit and cost per average treatment duration.
2. Context of the proposed cost: potential clinical benefits provided (including quality-of-life benefits) and potential economic benefits (including savings or cost offsets).
3. Shortcomings of other therapies.

Briefly present results of any observational research or economic data, with inclusion of the per-member per-month (PMPM) or incremental cost-effectiveness ratio result at minimum. Briefly summarize other published information on the cost or economic impact of the product (e.g., effect on resource utilization or other cost offsets).

Include the economic impact of special handling, delivery, route and site of administration, therapeutic drug monitoring, Risk Evaluation and Mitigation Strategy (REMS) programs, and other administrative offsets that would be above and beyond the cost of the product.

1.3B CONCLUSIONS

Summarize the value of the proposed product. Highlight key points regarding the clinical and economic advantages and uniqueness of the product. Finally, based on the information presented in Sections 2.0B through 5.0B that follow, the conclusions should include a statement regarding the expected effect of the product relative to other available treatment options, both pharmaceutical and nonpharmaceutical.

2.0B Product Information and Disease Description

2.1B PRODUCT INFORMATION

The recommended length of Section 2.1B is five pages (maximum 10). This section can be written in a paragraph or as a table. Brevity should be considered when writing

this section. When possible, hyperlink to the prescribing information/PI or use language from the highlights section of the prescribing information/PI.

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

- Generic name
- Brand name
- FDA-approved indication(s) and approval date
- Therapeutic class and/or mechanism of action
- Dosage forms and strengths
- Contraindications
- Boxed warnings, warnings/precautions, REMS
- Adverse events
- Unique identifiers (e.g., National Drug Code [NDC] number, American Hospital Formulary Service [AHFS] information)
- Wholesale acquisition cost (WAC) pricing
- Healthcare Common Procedure Coding System (HCPCS) code(s)

Other differentiating attributes may also be included, when clinically necessary, including the following:

- Pharmacology, 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)
- Administration (e.g., required health care provider administration or self-administration after provider training)
- 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.

For DTx products, complete all relevant product description information in addition to the Table of Highlights for Digital Therapeutics (Table 2.1.1B).

TABLE 2.1.1B

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	- Patient setting (home, work, school) - Health care setting - Institutional setting (nursing home, long-term care)
Intended line of business	- Commercial, Medicare, Medicaid, Other
Relationship to other therapies	- Stand alone - Add-on therapy to standard of care - Replaces existing therapy - Co-prescribed with pharmacologic therapy
Language	- Languages the product is available in
Considerations for specific populations	- Additional information on cultural, disability, age, health, or digital literacy requirements
Patient access to the product	- Formal prescription from a qualified clinician (in-person or virtual engagement) - Clinician referral for a nonprescription DTx product (in-person or virtual engagement) - Direct authorization by an employer for a nonprescription DTx product - Direct authorization by a payer for a nonprescription DTx product - "Authorized clinical protocol" established by an 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	- Offline-capable - Broadband
Compatibility	- PC/Mac - Browser (e.g., Chrome, Edge, Safari) - Operating system (e.g., iOS, Android)
Technical assistance availability	- In-app support via chat or call center availability

DTx = digital therapeutics; FDA = U.S. Food and Drug Administration; HCDM = health care decision-maker; iOS = Apple operating system; PC/Mac = refers to computers running IBM-based operating systems/computers produced by Apple.

2.1.2B 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 or appropriate clinical data (e.g., published literature, medical meeting abstracts) with the primary comparator products in the same therapeutic area generally including, but not limited to indications, contraindications, dosing, boxed warnings, warnings/precautions, adverse events, and other differentiating characteristics (expand as appropriate for the therapeutic class). This information should generally come from the highlights section of the PI. 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, comparative information to the reference product and other biosimilars should be included as well as evidence that demonstrates biosimilarity or interchangeability.

2.2B 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.

2.2.1B DISEASE DESCRIPTION

The disease description should be a top-line overview focusing on the indicated population.

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 U.S. patients. Present a summary of information from the literature for topics, including, but not 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. Disparities in access and utilization and outcomes experienced, as related to social and demographic factors such as race, ethnicity, gender, income, and

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.

2.2.2B APPROACHES TO TREATMENT

The key questions to address are the following: 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 versus repeating information.

1. Summarize current approaches to treatment (drug and nondrug), including where this product fits in with existing therapies and addresses 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, real-world evidence, 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 the heterogeneity of treatment effect, if any, related to the use of the product. Hyperlink to Section 3.0B for specific findings. Response to therapy may vary from patient to patient. HCDMs need to consider variability between individual patients, within populations studied, and between clinical studies. 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). This information should be provided where feasible; when not feasible to do so, the rationale should be provided.
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 Section 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 ensure 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 a REMS alongside other elements, describe it in Section 2.2.2B(5) and note in Section 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 HCDM 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 3.0B for specific findings.
8. Other key assumptions and their rationale.

2.3B EVIDENCE FOR CDTs

Drug Dossier with CDTs

When a CDT has been co-developed with a drug, or when the CDT is required per FDA labeling, then the four key evidence elements from the ACCE framework²⁶—analytical validity, clinical validity, clinical utility, and economic

value—will generally be captured in the drug dossier. As such, the drug dossier should contain information about the CDT according to Sections 2.3.1B and 2.3.3B.

CDT Dossier

In cases where the CDT is not inherently tied to the drug or if the CDT is not owned by the manufacturer, then the CDT developer may respond to an unsolicited request with a separate CDT dossier. A stand-alone CDT dossier should contain information about the CDT according to Sections 2.3.1B, 2.3.2B, and 2.3.3B. The CDT dossier should also contain an Executive Summary (Section 1.0B). If relevant and available, information that belongs in Section 4.0B and Section 5.0B may be supplied using the unapproved product, approved product, or unapproved use dossier templates.

2.3.1B PRODUCT INFORMATION FOR CDT

The recommended length of Section 2.3.1B is five pages (maximum 10). The following are components that should be supplied:

1. Generic name, brand name, manufacturer, or clinical laboratory.
2. Type of test: technical (e.g., immunohistochemical [IHC], fluorescent in situ hybridization [FISH], gene expression profile, sequencing panel).
3. Target: describe test target (e.g., biomarker).
4. Indications/uses with companion pharmaceutical that are cleared or approved by the FDA.
5. Date of FDA clearance or approval.
6. Intended use: clinical basis for CDT (e.g., treatment guidance, diagnosis, prognosis and management, risk management, treatment, monitoring, or pre-symptomatic testing).
7. Indication and target populations; prevalence of disease/condition, and CDT variant/marker prevalence in indicated population.
8. Place of CDT in drug therapy.
9. Contraindications, warnings/precautions, and interactions relative to CDT use.
10. Alternative tests and options available, whether they are CDTs or laboratory-developed tests; describe relative advantages and disadvantages.
11. Other key assumptions and their rationale.
12. Supporting clinical and economic evidence for the test, using the ACCE framework²⁶:
 - Analytical validity: How well does the test identify the target or biomarker it is intended to identify?
 - Is the accuracy with which a particular genetic or phenotypic characteristic identified within professional standards and federal regulation requirements?

- Sensitivity: How often is the test positive when the marker is present?
- Specificity: How often is the test negative when the marker is not present?
- Accuracy: How often is the test correct?
- Precision: Reproducibility of the test.
- Clinical validity: How well does the test identify the disease or medical condition of interest?
 - Positive predictive value: How often does a patient who tests positive have the medical condition?
 - Negative predictive value: How often does a patient who tests negative not have the medical condition?
 - Thresholds used to separate a positive from a negative result.
 - In which populations has the test been validated, and in how many studies?
- Clinical utility: How does the test improve patient outcomes?
 - Interventions that are based on positive and/or negative test results.
 - Efficacy/effectiveness and safety of the clinical intervention implemented as a result of the test.
 - Changes in patient outcomes, treatments received, clinical events, effect on disease progression, risk-benefit assessment, morbidity, quality of life, and survival, etc.
 - Consider inclusion of quantitative risk-benefit decision-analytic modeling.
- Economic value: What is the economic value of the test?
 - What is the expected difference in costs and outcomes compared with the next best alternative, including cost offsets from changes in drug utilization, side effect treatment, and other health care services and health outcomes?
 - The economic analysis should include, among other aspects, the prevalence of the condition, prevalence of the CDT marker of interest, and burden on the patient or health care system to collect and process the biological sample.
 - Include incremental cost per diagnosis, treatment modification, events avoided, life-years saved, and quality-adjusted life-years (QALYs) gained, etc.
- 13. Packaging description, regulatory codes, classifications, and identifiers.
- 14. Billing and reimbursement codes and price.
- 15. Copy of the product label or PI.

2.3.2B PLACE OF CDTs IN CLINICAL PRACTICE

The recommended length of Section 2.3.2B is 10 pages (maximum 15). For stand-alone CDT dossiers, include the

following information:

1. Disease description.
 - Epidemiology and relevant risk factors.
 - Pathophysiology.
 - Clinical presentation.
 - Societal and economic impact of disease.
2. Approaches to treatment.
 - Diagnosis (principal options, practice patterns, alternative options).
 - Anticipated use of the test in patient management.
 - Prognosis (e.g., expected intermediate health outcomes, expected net health outcomes of treatment).
 - Relevant clinical practice guidelines, clinical pathways, HTAs, and systematic reviews.
 - Other key assumptions and their rationale.

2.3.3B SUPPORTING CLINICAL DATA FOR CDT

The recommended length of each study summary is two pages (maximum five). The recommended length of a row in the evidence table is one page (maximum two) for each study.

For drug dossiers, studies pertaining to the CDT that do not belong in Section 3.0B should be summarized in this section.

For stand-alone CDT dossiers, all clinical trials that include the CDT should be summarized in this section.

Submit summaries of key studies that have been conducted (and discussed with the FDA), whether published or not. For example:

1. Analytical validation studies.
2. Clinical validation studies.
3. Clinical utility studies (e.g., randomized trials, prospective effectiveness trials, case series, retrospective studies, systematic reviews, meta-analyses).
4. Outcomes studies (e.g., decision-analytic modeling studies; prospective, trial-based cost-effectiveness studies; cross-sectional or retrospective costing studies and treatment pattern studies; systematic review articles; patient-reported outcomes studies, quality-of-life studies).
5. Safety studies.

Evidence in summaries should include the following:

1. Setting and location of study.
2. Study design and research question(s).
3. Inclusion and exclusion criteria.
4. Patient characteristics (demographics, number studied, disease severity, comorbidities).
5. Intervention and control groups.
6. Patient follow-up procedures (e.g., if an ITT design is used, were drop-outs followed and for what time period?) and treatment/follow-up period.

7. Clinical outcome(s) measures.
8. Outcomes evaluated.
9. Delineate primary versus secondary study endpoints and their corresponding results.
10. Other results/outcomes reported (e.g., quality of life, assay performance).
11. Principal findings.
12. Statistical significance of outcomes and power calculations.
13. Validation of outcomes instrument (if applicable).
14. Compliance behavior.
15. Generalizability of the population treated.
16. Relevance to enrolled populations.
17. Publication citations/references used.
18. State whether trials or other studies for the product are registered in a public trial registry and, if so, provide access information (e.g., ClinicalTrials.gov).

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 3.0B 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 legacy product, there may be a very large number of studies in the medical literature, so inclusion of every study may be impractical for both manufacturers and HCDMs. In such cases, it is important that the manufacturer exhibits 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 clinical information should be provided on the first page of Section 3.0B.
2. Pivotal data, and in some instances other RCTs and/or real-world evidence, that contribute significantly to the knowledge base of the product should be included as *study summaries* (see Section 3.1B) and *evidence tables* (see Section 3.2B).
3. Informative but smaller and/or less rigorous studies that may add to the evidence base should be included as *evidence tables* (see Section 3.2B) 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 Section

3.0B 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 participants, 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. Because 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 participants represent the target population as described in Section 2.2.1B and identify differences that may obscure translation to real-world effectiveness.

For clinical trials, the representation of study participants to real-world populations should be explained. Supplemental tables depicting representation are strongly encouraged. Retrospective studies should include subgroups disproportionately affected by the health condition if such data are available, and limitations that erode generalizability should be disclosed.

Considerations for Section 3.0B:

- 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 a 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 Section 3.0B. 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 or yield varied outcomes, 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. Retrospective studies can be a valuable source of information about diverse subgroups and therapeutic variability; however, many measures of diversity such as race, ethnicity, and socioeconomic status are not consistently available in retrospective databases. In cases where health disparities cannot be examined, the rationale for omitting this information should be provided.

- 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 from peer-reviewed 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 Section 3.0B. 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 scientific podium 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 participants. 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 “break-through 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, and comparison with innovator agents, etc., are especially important, all relevant 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 Section 3.0B should not be restated in Section 5.0B.

3.1B STUDY SUMMARIES

The recommended length of each study summary is five pages (maximum ten). Study summaries should include the following items where available and applicable:

1. Publication citations, study name, ClinicalTrials.gov ID number, sponsor, or funding source.
2. Objective, location, and study start and completion dates.
3. Trial design, randomization, and blinding procedures.
4. Setting, inclusion, and exclusion criteria.
5. Baseline patient characteristics and demographics.
6. Drop-out rates and procedures for handling drop-outs (e.g., ITT, per protocol).
7. Treatments and interventions, dosage regimens, washout period, concomitant therapies, and relevant pre/post-protocol care, etc.
8. Clinical outcome(s) evaluated, measured, and collected, delineating primary versus secondary endpoints as well as pre-specified versus post hoc.
9. Measures of effect (e.g., risk difference, risk ratio, odds ratio, number needed to treat), statistical significance of outcomes, and power calculations.
10. Validation of outcomes instruments, if applicable.
11. Generalizability of the population treated.
12. Study limitations, as stated by the authors.

3.2B EVIDENCE TABLES

The recommended length of a row in the evidence table is less than one page (maximum two) for each study. Evidence tables should include the following data elements:

- Citation (if unpublished, give abstract information or indicate “data on file”)
- Treatments
- Sample size and length of follow-up
- Inclusion and exclusion criteria
- Design
- Primary endpoints
- Secondary endpoints
- Results (provide an explicit statement of effect size, not just relative risk reduction and statistical significance. Within the Results column, include a table of key results)
- Statistical significance (e.g., p-value and confidence interval)

It may be helpful to display evidence tables in landscape rather than portrait formats with appropriate use of abbreviations and other acceptable ways to display data in a clear, objective, and concise way.

4.0B Economic Value and Modeling Report

The recommended length of Section 4.0B is 12 pages (maximum 20) for each model.

4.1B MODELING OVERVIEW

This section presents an overview of the rationale, approach, and suggested methods for developing economic models. The intent of the model is to quantify for the HCDM the risk-benefit trade-off of the product and its economic value.

4.1.1B USE OF MODELING FOR DECISION-MAKING

Available data on the clinical benefits and harms and economic impact of the product under consideration are provided in Sections 3.0B and 5.0B of the Approved Product Dossier and are the core of evidence-based decision-making. Most of the source data for models are in Section 3.0B, whereas Section 5.0B contains data from external sources such as clinical practice guidelines and prior HTAs. Additional data may exist in the form of real-world evidence which may also provide source information for economic modeling. These data, however, may have important limitations for decision-making. For example:

1. RCTs may not include all relevant comparator interventions.
2. The duration of follow-up in RCTs may be limited.

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

These limitations have led to recent efforts in CER to improve the quantity, diversity, and relevance of information available to HCDMs. Comparative effectiveness data—derived from studies including relevant populations, comparators, and outcomes—will prove valuable to HCDMs and should be reported in Sections 3.0B and 5.0B of the Approved Product Dossier. These data are more likely (and should be expected) to be available for more mature products. In addition, evidence may be generated through pay for performance or coverage with evidence development schemes. Synthesis and evaluation of these data will remain challenging, however, and are unlikely to be available for new products.

Cost-effectiveness models based on decision analytics are an effective means to assess the overall potential value of health care technologies. They are disease-based and consider the effect of the new technology on the clinical outcomes for the target population. Typically, they include evidence on the incidence of the disease or condition in the target population, the medical care required to diagnose and treat the disease, the relative and absolute risk reductions offered by the technology, survival and quality-of-life effects, and the costs of the interventions. Decision models can provide the following:

1. An explicit framework for decision-making.
2. A synthesis of evidence on health consequences and costs from different sources.
3. A formal assessment of uncertainty.
4. A quantitative measure of clinical risk-benefit.
5. Explicit and evaluable assumptions.
6. Specificity for a product’s role or place in therapy.
7. Benchmarks against which the product’s future performance can be measured.

Models are not without challenges. In particular, because of the complexity and inherent required assumptions, models can be perceived as a “black box” approach or biased. The AMCP Format has been developed to help address these limitations by providing a consistent format for conducting and reporting cost-effectiveness models to improve their transparency and acceptability.

Manufacturers should consult with HCDMs, ideally in the early phases of model development, to identify optimal modeling approaches and ensure the incorporation of appropriate comparator products, target populations, and endpoints to reflect clinical reality and HCDM needs.

4.1.2B TYPES OF MODELS

There are several types of models that can be helpful to HCDMs, including cost-effectiveness models, budget impact models, and financial models.

Cost-effectiveness Models

Cost-effectiveness models address the question “Is the technology good value for the money?” The focus of the Approved Product Dossier is the clinical and economic value of products for plans and their members. Evaluations that include effects on patients (e.g., morbidity and mortality) and on health care costs are thus most relevant and termed in general “cost-effectiveness models.” These models are primarily useful for assessing the overall clinical risk-benefit and economic value of a product in relation to products in its class and other health care interventions in general and are the primary focus of this section. Cost-effectiveness models use clinical data and can be relatively complex and thus should follow the recommendations in this section, as well as best practices published by ISPOR Society for Medical Decision Making (SMDM) Modeling Good Research Practices Task Force.^{42,65-70}

Budget Impact Models

Budget impact analyses address the question “Is the technology affordable to the health system?” A budget impact model estimates “the expected changes in the expenditure of a health care system after the adoption of a new intervention.”⁷¹ Budget impact models are not intended to establish the overall value of health care technologies because they do not include the full long-term effects of the technology on clinical and patient outcomes. They can be useful for estimating systemwide (e.g., pharmacy and medical) budget impacts, however, and are commonly used by HCDMs. These models, as defined here, estimate the target population, drug/product costs, health care cost offsets, and adverse event costs, as well as the expected utilization in the health care system, to derive projected PMPM and overall cost impacts. Budget impact models use clinical data, including real-world evidence, and can be relatively complex so they should follow the recommendations in this section and best practices published by ISPOR.^{71,72}

Financial Models

Financial models provide an estimate of the financial impact of new technology on the pharmacy budget only because they typically include drug/product costs, network or other discounts, rebates, cost-sharing, and other benefit design effects, but no evaluation of clinical effects or other economic consequences. HCDMs usually have the necessary internal resources to develop such models. Although these models may be useful for negotiations between manufacturers and HCDMs, they are not central to the evidence- and value-based decision-making process and are not addressed further in the AMCP Format. Financial models are not required but may be included in the dossier at the discretion of the manufacturer.

4.1.3B OTHER CONSIDERATIONS

1. A clear, written statement of the decision problem, modeling objective, study perspective, and scope of the model should be developed. This should include the spectrum of disease considered, target population, alternative interventions, health and other outcomes, and time horizon.
2. ISPOR and SMDM have produced comprehensive guidance related to various aspects of modeling.^{42,65-70} ISPOR-SMDM best practices should be followed when applicable.
3. When a product is intended for treatment of more than one disease or indication, its effect should be modeled for each, unless a reasonable case can be made for a single model, such as may be the case for budget impact models.
4. Models that have been previously developed may be adapted for use according to the AMCP Format. An existing model should be modified to follow the general framework described in this document and must be able to demonstrate the systemwide effect of introducing the product to health care system formularies. Evidence supporting the validity of existing models should be provided, as well as sufficient documentation and transparency on their design, functioning, and data inputs.
5. Cost-effectiveness analyses conducted alongside RCTs, particularly when of sufficient size and follow-up, can provide useful and sometimes substantial evidence of economic value. Cost-effectiveness models should be considered complementary to such studies, allowing for the adjustment of health care resource use, unit costs, effectiveness, and practice patterns.
6. Real-world evidence studies can provide additional insights from larger populations in more realistic

conditions that may be more generalizable to practical use but should be supplemental to efficacy/safety data gathered from well-designed RCTs.

7. All assumptions should be clearly presented.
8. Drugs administered by health care providers should generally be considered in a similar manner to traditional pharmaceutical products. Additional considerations may be required for site of care (e.g., inpatient, home infusion, outpatient infusion center).
9. Because of similarity to their reference product, biosimilars generally do not require the development of specific cost-effectiveness models. Budget impact models or cost-minimization analyses may be more relevant.
10. When possible, a stand-alone, electronic, unlocked, modifiable model should be provided to HCDMs. The use of commonly available software (e.g., Microsoft Excel) is recommended. The model should be interactive and flexible, allowing the user to choose which inputs to include in the model and tailor inputs to the health system or health plan.
11. Key limitations of the model should be disclosed, particularly those involving the representation of important patient subgroups, and generalizability to real-world populations.
12. Users of this document should recognize that the AMCP Format is a set of recommendations for the types of evidence and reporting formats that are likely to be useful for HCDM. The need for flexibility is recognized by AMCP, however. Specific requirements are determined by individual HCDMs and may consist of data requests or methods beyond those outlined in this document.

4.2B COST-EFFECTIVENESS ANALYSIS

4.2.1B APPROACH AND FRAMEWORK

Guidelines

In general, the cost-effectiveness framework should consider recommendations published by ISPOR and SMDM Modeling Good Research Practices Task Force.^{42,65-70}

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 safety.

5. Outcomes of therapy for each clinical pathway.
6. Cost and outcomes analysis presented in cost/consequences tables and as incremental 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 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, 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).⁷³

4.2.2B DATA SOURCES

The identification, selection, interpretation, and use of data to inform the model are key to the modeling process and should receive ample attention from model developers and users. The analysis should be based on the highest-quality and most up-to-date clinical, epidemiologic, patient, and economic data available from the sources most relevant to the model. The process for identifying, evaluating, and selecting 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 significant safety signals derived from other study types (e.g., observational studies and/or real-world evidence). The economic impact of treatment-related adverse events should be incorporated into cost-effectiveness analyses. A wide range of estimates should be explored given the challenge of accurately ascertaining the likelihood of low-probability events.

Economic Data

Unit cost data ideally would be relevant to HCDMs, based on health care system data. If specific health care system data are not available, costs from representative U.S. private payers, Medicare, and 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 methodology should clearly explain how the model addresses patient cost-sharing for the treatment(s) evaluated and assumptions about patient adherence.⁷⁰

Utilities

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

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 a clear description of the methodology will be necessary for health care system staff to evaluate the validity of this approach.

Real-World Evidence

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

4.2.3B CONDUCT

Base-case Estimates

The expected (average) clinical and economic outcomes should be calculated for each strategy evaluated, as well as incremental costs and effectiveness. Differences in the absolute risk of events should be determined, and health care cost offsets versus drug costs should be displayed independently and combined. Clinical risk-benefit trade-offs should be explicitly presented and discussed.

Sensitivity Analysis

Because cost-effectiveness models are simplified views of disease processes, specifying the model structure is important. Developers of such analyses should employ established model frameworks, if available, and seek input from clinicians to ensure that models have good face validity for the disease or condition being evaluated.

Both deterministic and probabilistic sensitivity analyses should be conducted to assess the robustness of the results. Analysts should identify the distribution used for each parameter that is included in a probabilistic sensitivity analysis. One-way sensitivity analyses of all key parameters in the model are also strongly recommended, including assessment of effects on both incremental effectiveness (e.g., QALYs) and cost-effectiveness. Use

of generally accepted confidence levels (95%) should be employed if parameter uncertainty is, at least largely, characterized by random error. The use of tornado diagrams is encouraged to identify the most influential parameters. The parameters and assumptions that have the greatest effect on the results should be identified. Scenario analyses testing the assumptions used in the model are also highly recommended. Generation of cost-effectiveness scatter plots and acceptability curves are recommended to display the results of the analysis.

4.3B BUDGET IMPACT MODEL

4.3.1B APPROACH AND FRAMEWORK

Guidelines

The modeling approach and analytic framework of the budget impact model should generally follow the guidance provided by ISPOR.^{71,72}

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

1. Characteristics of a health system, such as prevalence and incidence of disease among the population and restrictions to access.
2. Use and cost of current mix of therapies used to treat the condition.
3. Projected use and costs of the new mix of therapies to treat the condition.
4. Costs and cost offsets associated with change in use of condition-specific health services.

Perspective and Time Frame

The perspective of the HCDM organization is recommended. The time horizon of the model should be of relevance to the HCDM, typically one to five years.

Population

The target population for a budget impact model should include all patients eligible to receive the new intervention during the modeled time horizon.

4.3.2B DATA SOURCES

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

4.3.3B CONDUCT

Results

When reporting the economic impact of the intervention, it is recommended to present the findings as both the

PMPM cost difference and the overall budget impact on the health system. Results may also include cost per-treated member per-month (PTMPM).

Sensitivity Analysis

Sensitivity analyses are recommended for assessing parameter uncertainty within the budget impact model. Scenario analyses are recommended to assess structural uncertainty in model design and assumptions.

Any expected off-label use of the new health technology should not be included in the main budget impact analysis but may be considered in scenario analyses.

4.4B MODELING REPORT AND INTERACTIVE MODEL

4.4.1B TRANSPARENCY

Transparency and clarity of presentation are a necessity. The need for and value of transparency is widely recognized and can provide some protection against bias and error. Model transparency serves the important purpose of providing both a high-level overview of the model structure, components, and outputs, as well as detailed documentation for users interested in evaluating the technical elements of the model.⁶⁶ Therefore, manufacturers are encouraged to focus efforts on the clarity and transparency of results. Detailed descriptions that explain the flow of data through the model are recommended. All calculations should be explained in a simple, straightforward manner to allow a non-health economist to comprehend the analysis. The information and references should be accessible in the report format, as well as shown directly in the model to optimize ease of review.

4.4.2B MODELING REPORT FORMAT

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

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

Figure 1. Provide a figure displaying the structure of the model (e.g., a decision tree, Markov model, budget impact model). A simplified schematic diagram may be used for ease of presentation, but a detailed figure should also be included.

Table 1. Provide a table listing all the model inputs, including probabilities, costs, and utility estimates if

appropriate. Provide a range of values on which sensitivity analyses are based for each input.

1. Include references in the table for all inputs, including ranges.
2. Note in the table any estimates that lack supporting evidence.

Table 2. Provide an explicit list of model assumptions, including assumptions about comparator interventions, clinical events, patient management, delivery, administration, setting of care, and costs.

Table 3. Present the disaggregated results in a table (e.g., cost-consequence style, with costs presented separately from health outcomes). Data presented in this format are more easily understood and interpreted by health care system formulary committees. The following specific data should be presented for each strategy as appropriate for the analysis type:

1. The projected clinical events (e.g., heart attacks, cirrhosis, recurrence).
2. The life expectancy, QALY estimates, or other measured outcomes.
3. Total health care costs.
4. The cost of implementing therapy, including all anticipated costs of care management, delivery, administration, and setting of care, and the resulting cost offsets.
5. Model results as appropriate for the model type (e.g., incremental cost-effectiveness ratios, PMPM estimates of budget impact).

Figure 2. Present one-way sensitivity analyses on all model inputs in a figure (e.g., tornado diagram) or a table.

1. Clearly present the model inputs or assumptions that drive the difference in (1) costs, (2) effects, and (3) incremental cost-effectiveness.
2. When appropriate, present multiway (e.g., two-way, best- and worst-case scenario, probabilistic) sensitivity analyses.

CHEERS Guidance

In addition to the general guidance provided above, a notable addition to the scientific literature related to reporting standards for economic evaluations published since our last AMCP Format revision is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.⁷⁴ This statement provides additional guidance regarding preferred reporting standards for economic evaluations and may serve as an additional resource to model developers.

4.4.3B INTERACTIVE MODEL

Model Characteristics

To improve transparency and ease of use, it is

recommended that models be implemented in spreadsheet software. Other software packages should only be used if the user (1) is familiar with them, and (2) agrees with the manufacturer about their use. Custom software models are generally discouraged but may be suitable if clearly documented in peer-reviewed publications and a user's manual. Interactive models should have the following characteristics:

1. All data and calculations relevant to the economic model should be contained in the spreadsheet and visible to the user.
2. All key inputs should be modifiable by the user.
3. To the extent feasible, the model, its logic, and its calculations should be clear and self-documenting, using best practices for formatting, comments, and explanatory guides such as text boxes.
4. The model allows for analysis of relevant subpopulations (age, sex, comorbidities) where applicable.
5. The model allows the health care system to incorporate its own data (e.g., membership size, prevalence rates, cost estimates) in place of default data, such as national norms.
6. The model provides automated one-way sensitivity analysis.

Model Accessibility

It is recommended that the health care system require that an interactive model be made available electronically (e.g., Microsoft Excel), preferably after meeting with the manufacturer to review and discuss its design, key assumptions, base-case results, sensitivity analyses, and practical application. If the manufacturer will not provide an interactive model for the HCDM's use, a clear statement to this effect and standing policy should be provided in the modeling report. Alternative approaches include interactive modification of the model with a representative of the manufacturer without providing a leave-behind version of the model, although such arrangements are less desirable. Manufacturers are also encouraged to publish economic models in the peer-reviewed literature and update the models and publications with real-world evidence as available.

Model users should recognize that input parameters must be plausible, and many combinations of inputs in complex models will not be self-consistent. Thus, users should modify model inputs based on available data and reasonable assumptions.

5.0B 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 U.S.

5.1B 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 from the U.S. that are specific to the product, its comparators, 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.

5.2B 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 AHRQ and PCORI, reports from ICER, and HTAs from recognized public or private organizations, including international bodies such as NICE and CADTH. Summarize the information that is relevant to the product.

5.3B 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.

5.4B 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, productivity studies, and 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, cost per life-years gained, cost 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).

5.5B EFFECT ON EQUITY

RCTs and cost-effectiveness analyses typically do not address barriers to the equitable use of a new drug or device. Such barriers may include, but are not limited to, access to specialists, health disparities and social barriers, stigma, and the patient's ability to afford and utilize a medication. While health equity data for new interventions may initially be very limited, equity considerations often have implications for value assessment and should be discussed.

5.6B EFFECT ON QUALITY MEASURES

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, this section is not applicable.

5.7B 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' families and caregivers. If no information exists, this section is not applicable.

6.0B Dossier Appendices

The following information is valuable to HCDMs and should be included in Section 6.0B, where possible.

6.1B REFERENCES CONTAINED IN DOSSIERS

Include citations for all known published clinical and economic studies in the bibliography section. Reprints of relevant published studies should be available on request and, where possible, should provide links to original sources if they are free.

6.2B ECONOMIC MODELS

Include economic models.

6.3C PRODUCT PRESCRIBING INFORMATION

Include the FDA-approved PI and instructions for use for the approved uses of the product.

6.4C PATIENT INFORMATION

Include any patient information, such as patient PIs and medication guides, for the approved uses of the product.

6.5B MATERIAL SAFETY DATA SHEET

Include or link to a Material Safety Data Sheet for the product.

6.6B APPENDICES SPECIFIC TO DTX PRODUCTS

Privacy and data security

Information related to privacy and security is required to be included in an AMCP dossier. Although the intended audience of the dossier is HCDMs who may lack the expertise needed to thoroughly evaluate the privacy and data security specifications for DTX products, a thorough evaluation of privacy and data security is required, since this is essential to a comprehensive evaluation. Moreover, a review of privacy and safety may be performed prior to an evaluation of the clinical evidence by a P&T committee or body. If needed, HCDMs may seek additional expertise

from data information technology/security experts, establish a DTx subcommittee, or have a separate group (such as an innovation center), and assist with DTx evaluation. DTx manufacturers may work directly with HCDMs to integrate and implement DTx. Manufacturers may also provide relevant links to related information (i.e., privacy policies, terms of service).

Items to be addressed in a privacy and data security appendix include the following:

- Certifications (e.g., SOC 2, HITRUST, PCI DSS, ITIL, ISO 27001, CIPP)
- Data encryption: software supports SSL encryption
- Antivirus software
- Data protection security measures
- Security information and event management solutions (SIEM), web application firewalls (WAF), SECOPS monitoring, managed security providers (MSSPs), security orchestration automation and response platforms (SOAR)
- Data backup and recovery solutions
- Details on where data are stored
- Processes for secure disposal of information technology equipment and media
- Intrusion detection systems (IDS) or intrusion prevention systems (IPS) used

- Parental restrictions for minors
- Data integrity
- Cybersecurity
- Data privacy processes
- Multifactor authentication
- Ransomware protection
- Other hack prevention methods

Engagement

Manufacturers may specify how they define engagement in an optional appendix. Due to the wide variety of DTx products 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 DTx products. If engagement measures were used in clinical trials or real-world evidence, they may be addressed in Section 3.0B or Section 5.0B.

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 health care professionals may also be included.

Evidence Recommendations for Unapproved Use Dossiers

SECTION 1.0C – HIGHLIGHTS AND OVERVIEW

SECTION 2.0C – PRODUCT INFORMATION AND DISEASE DESCRIPTION

SECTION 3.0C – CLINICAL EVIDENCE

SECTION 4.0C – ECONOMIC VALUE AND MODELING REPORT

SECTION 5.0C – ADDITIONAL SUPPORTING EVIDENCE

SECTION 6.0C – DOSSIER APPENDICES

1.0C HIGHLIGHTS AND OVERVIEW

The recommended length of Section 1.0C is two pages (maximum four).

This section provides an at-a-glance overview of the key information about an unapproved use of an approved product for which the manufacturer is seeking approval from the FDA.

Manufacturers may not make claims about an unapproved

use of an approved product. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved use. Manufacturers may provide factual and objective information about the unapproved use in an Unapproved Use Dossier.

Just as with the Unapproved Product Dossier, there is no Executive Summary in an Unapproved Use Dossier because the intent of an Executive Summary is to convey the overall value proposition of a product based on clinical and economic evidence. In an Unapproved Use Dossier, no characterization or conclusions should be made regarding the safety or effectiveness of the unapproved use of an approved product. However, key information should be included about the unapproved use, using the Table of Highlights for Unapproved Use of An Approved Product (Table 1.1C).

It is important to acknowledge that information may or may not be available depending on the phase of clinical studies for the unapproved use during the post-marketing period of an approved product. If information is not yet

available or cannot be disclosed per the manufacturer's discretion, indicate "N/A." As information becomes available for communication, the manufacturer should update

the dossier.

Be brief and concise. Provide citations and references to indicate the source of information where applicable.

TABLE 1.1.C

TABLE OF HIGHLIGHTS FOR UNAPPROVED USE OF AN APPROVED PRODUCT

Type of Information	Description of Information
Revision dates	List the dates of revisions to this table in reverse chronological order
Manufacturer name	List the names of companies involved in developing and marketing the unapproved use
Approved product name	List the names of the approved product (brand, generic, chemical name)
Drug class	Describe the drug class in which the product belongs
Unapproved use	List the diseases, indications, and target populations for which the unapproved use is being studied and FDA approval is being sought
Approved use and indication	List the FDA-approved uses and indications for the approved product
Special FDA designations	List special designations per FDA (e.g., fast track, orphan, breakthrough) and the date of designation; provide links to source information (e.g., FDA, press release)
FDA submission date	List the date of NDA/BLA submission to the FDA
FDA Advisory Committee meeting	List the date of the planned or anticipated FDA Advisory Committee meeting
Original FDA approval date and anticipated approval date	List the original date of FDA approval for the product and the date or time frame (e.g., year, quarter) of anticipated FDA approval for the unapproved use
Approval dates and indications in other countries (outside of the U.S.)	List other countries and (anticipated) approval dates and indications
Phase 3 trials related to unapproved use completed	List the name or citation of trials and dates completed, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Phase 3 trials related to unapproved use in progress	List the name or citation of trials and dates in progress, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Phase 2 trials related to unapproved use completed	List the name or citation of trials and dates completed, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Phase 2 trials related to unapproved use in progress	List the name or citation of trials and dates in progress, key endpoints, and number of patients; provide links to ClinicalTrials.gov or PubMed
Anticipated routes and dosing information	Describe the route(s) of administration and dose(s) for the unapproved use of the product that were used in clinical trials and anticipated to be approved by the FDA
Anticipated location/settings for product administration	Describe the location or health care setting where the unapproved use product was administered in clinical trials and anticipated to be given when approved by the FDA
Prevalence of condition associated with unapproved use in the U.S.	Express results per 100,000 (e.g., 1 per 100,000 women, 5 per 100,000 live births, 10 per 100,000 per year)
Annual incidence of condition associated with unapproved use in the U.S.	Express results per 100,000 (e.g., 1 per 100,000 women, 5 per 100,000 live births, 10 per 100,000 per year)
Product pricing information	List the price of the approved product
Anticipated patient support programs	Describe potential plans for patient support programs
Anticipated distribution strategy	Describe any anticipated changes to distribution of the unapproved use product

FDA = U.S. Food and Drug Administration; sBLA = supplemental biologics license application; sNDA = supplemental new drug application; U.S. = United States.

2.0C Product Information and Disease Description

2.1C PRODUCT INFORMATION

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

Manufacturers may not make claims about an unapproved use of an approved product. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved use. Manufacturers may provide factual and objective information about the unapproved use in an Unapproved Use Dossier.

Manufacturers are encouraged to provide as much detailed information about the unapproved use as possible. It is important to acknowledge that information may or may not be available depending on the phase of clinical studies for the unapproved use during the post-marketing period of an approved product. If information is not yet available or cannot be disclosed per the manufacturer's discretion, indicate "N/A."

As information becomes available for communication, the manufacturer should update the dossier regularly and revise the corresponding information in Section 1.0C Highlights and Overview.

The following are the components that should be included (per FDA Final Guidance,³ the PIE Act,⁴ and AMCP Format recommendation):

1. A clear statement that the product is not FDA approved for the proposed indication, and that the safety and effectiveness have not been established for the proposed indication.^{3,4}
2. Information related to the phase of product development (e.g., the status of any studies in which a product is being investigated and how it relates to the overall product development plan, whether a marketing application for the product has been submitted to the FDA, or when such a submission is planned).^{3,4}
3. Provide a link to the PI.
 - Provide the full FDA-approved prescribing information.
4. Product information for the unapproved use (e.g., drug class, device description, features).^{3,4}
 - Generic, brand, chemical, or other given name of the product.
 - Proposed mechanism of action.
 - Pharmacology, pharmacokinetic, and pharmacodynamic information.
 - Drug/drug, drug/food, and drug/disease interactions.
5. Dosing and administration information (usually from clinical trials).
6. Anticipated access and distribution information.
5. Information about the indication being sought, such as information from the clinical study protocols about end-points being studied and the patient population under investigation (e.g., number of participants enrolled, subject enrollment criteria, subject demographics).^{3,4}
6. Anticipated timeline for approval for indication being sought (e.g., FDA approval/clearance/licensure of the unapproved use of the approved product).^{3,4}
 - Date of new drug application (NDA), BLA, device pre-market approval (PMA), 510(k) submission for FDA clearance.
 - Date of FDA Advisory Committee review, if any.
 - Date of anticipated FDA approval/clearance/licensure.
7. Product pricing information.
 - See Section 4.0C
 - Information may be provided here and/or in Section 4.0C.
8. Patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).^{3,4}
9. Product-related programs or services (e.g., patient support programs).^{3,4}
10. Factual presentations of results from studies, including clinical studies of drugs or devices or bench tests that describe device performance (i.e., no characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved use for the approved product).
 - See Section 3.0C.
 - Information may be provided here and/or in Section 3.0C.
11. Information on FDA expedited approval.
12. Other factual information per the manufacturer's discretion that does not run afoul of other guidelines or restrictions.

For DTx products, complete the Table of Highlights for Unapproved Use of an Approved Product (see Section 1.1C) in addition to the Table of Highlights for Digital Therapeutics (Table 2.1.1C).

TABLE 2.1.1C **TABLE OF HIGHLIGHTS FOR DIGITAL THERAPEUTICS**

Type of Information	Description of Information
Product version	<ul style="list-style-type: none"> • Include version of application that the dossier applies to
Approval pathway	<ul style="list-style-type: none"> • 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) • Health care setting • Institutional setting (nursing home, long-term care)
Intended line of business	<ul style="list-style-type: none"> • Commercial, Medicare, Medicaid, Other
Relationship to other therapies	<ul style="list-style-type: none"> • Stand alone • 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
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 nonprescription DTx product (in-person or virtual engagement) • Direct authorization by an employer for a nonprescription DTx product • Direct authorization by a payer for a nonprescription DTx product • “Authorized clinical protocol” established by an 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	<ul style="list-style-type: none"> • Additional hardware or software required
Host technology and required hardware components (if applicable)	<ul style="list-style-type: none"> • 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 (e.g., Chrome, Edge, Safari) • Operating system (e.g., iOS, Android)
Technical assistance availability	<ul style="list-style-type: none"> • In-app support via chat or call center availability

DTx = digital therapeutics; FDA = U.S. Food and Drug Administration; HCDM = health care decision-maker; iOS = Apple operating system; PC/Mac = refers to computers running IBM-based operating systems/computers produced by Apple.

2.2C DISEASE DESCRIPTION

The recommended length of Section 2.2C is five pages (maximum 10) for each disease state.

It is understood that the exact indication of the product is not fully known until final FDA approval. Manufacturers may struggle with the depth and breadth of disease information to be presented without making characterizations or conclusions about the safety or effectiveness of the proposed indication. Nevertheless, HCDMs require a basic understanding of the disease when reviewing information

about the proposed indication for the product.

Manufacturers are requested to provide as much information as possible about the medical condition or disease state for which the proposed indication for the product is being studied and FDA approval is being sought without making characterizations or conclusions about the safety or effectiveness of this unapproved use. This is true especially with rare or orphan diseases. The intent is to give the reader a good overall sense of the disease. The disease description should be brief and should include epidemiology, risk

factors, pathophysiology, clinical presentation, and burden of disease (e.g., societal, humanistic, health care resource utilization, economic). Manufacturers should provide a description of specific patient subpopulations in which the unapproved use is being studied, if applicable. Include clinical markers, diagnostic or genetic criteria, or other markers, if known, that can be used to identify these subpopulations. Information may be sourced from clinical trials (e.g., target study population, inclusion and exclusion criteria, baseline characteristics) and from medical literature. Other sources may be used per manufacturers' discretion. Cite and reference all information.

3.0C Clinical Evidence

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

It is important that Section 3.0C is transparent and reflects the full body of clinical evidence that exists for a product. For the unapproved use, available evidence may be limited to a few studies, and inclusion of all studies in the dossier is sensible. 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 the evidence be separated into the following categories:

1. An overview of clinical information should be provided on the first page of Section 3.0C.
2. Pivotal data, and in some instances other RCTs and/or real-world evidence, that contribute significantly to the knowledge base of the unapproved use should be included as *study summaries* (see Section 3.1B) and *evidence tables* (see Section 3.2C).
3. Informative but smaller and/or less rigorous studies that may add to the evidence base for the unapproved use should be included as *evidence tables* (see Section 3.2C) only.
4. All other studies that have been reported but do not add significantly to the knowledge base of the unapproved use should be identified in a *bibliography* only.

The overview of the information contained in Section 3.0C should define a specific set of objective criteria for inclusion and exclusion of studies and describe how studies were selected for inclusion and exclusion. 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 participants, 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. Because these definitions may vary depending on the context of the product, clinical setting, incidence/prevalence of the disorder, and available treatment alternatives, 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 participants represent the target population as described in Section 2.2C 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 limitations that erode generalizability should be disclosed.

Considerations for Section 3.0C:

- 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 a 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 Section 3.0C. 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.
 - 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 peer-reviewed 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.

- If the results of a trial have been reported in more than one journal article or conference abstract, poster, or scientific podium 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 participants. Discuss important study findings and comment on their implications for different patient populations.
- Data summarized in Section 3.0C should not be re-summarized in Sections 2.0C and 5.0C.

3.1C STUDY SUMMARIES

The recommended length of each study summary is two pages (maximum five). Study summaries should include the following items where available and applicable:

1. Publication citations, study name, ClinicalTrials.gov ID number, and funding source.
2. Objective, location, and study start and completion dates.
3. Trial design, randomization, and blinding procedures.
4. Setting, inclusion, and exclusion criteria.
5. Baseline patient characteristics and demographics.
6. Drop-out rates and procedures for handling drop-outs (e.g., ITT, per protocol).
7. Treatments, interventions, dosage regimens, washout period, concomitant therapies, etc.
8. Clinical outcomes evaluated, measured, and collected, delineating primary versus secondary endpoints, as well as pre-specified versus post hoc analyses. When applicable, information on surrogate endpoints should also be provided (i.e., for expedited pathways).
9. Measures of effect (e.g., risk difference, risk ratio, odds ratio, number needed to treat), statistical significance of outcomes, and power calculations.
10. Validation of outcomes instruments (if applicable).
11. Generalizability of the population treated.
12. Study limitations, as stated by the authors.

3.2C EVIDENCE TABLES

The recommended length of a row in the evidence table is less than one page (maximum two) for each study. Evidence tables should include the following data elements:

- Citation (if unpublished, give abstract information or indicate “data on file”)
- Treatments
- Sample size and length of follow-up
- Inclusion and exclusion criteria
- Design
- Primary endpoints
- Secondary endpoints
- Results (provide an explicit statement of effect size, not

just relative risk reduction and statistical significance. Within the Results column, include a table of key results.)

- Statistical significance (e.g., p-value and confidence interval)

It may be helpful to display evidence tables in landscape rather than portrait formats with appropriate use of abbreviations and other acceptable ways to display data in a clear, objective, and concise way.

4.0C Economic Value and Modeling Report

The price of the product is already known for the approved product and should be included in the Unapproved Use Dossier. Product pricing information may help HCDMs consider the potential economic impact and consequences of the product. Describe any potential or anticipated changes of pricing expected if the proposed indication is approved by the FDA.

It is recognized that budget impact models and cost-effective models may not be feasible to construct or communicate before FDA approval of an unapproved use because such models rely on certain outcomes and assumptions regarding effectiveness and safety of the product. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved use of an approved product.

When deemed necessary, manufacturers may request execution of nondisclosure agreements so that sensitive or confidential pricing information may be shared or discussed in a manner that is protected.

Information on costs should be included, if anticipated to differ from the current price.

5.0C Additional Supporting Evidence

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

Section 5.0C should consist of all other types of evidence and studies that do not fit in Section 3.0C that support the unapproved use in a clear and concise format. Examples include clinical practice guidelines, HTAs and systematic reviews, compendia, modeling, and pharmacoeconomic and pharmacoequity studies. Although the indication has not been FDA approved, AMCP acknowledges that some of these data may be available (e.g., National Comprehensive Cancer Network [NCCN] may include recommendations based on the product being approved in the U.S.).

Similar to Section 3.0C, evidence reported in this section may include 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 U.S.

5.1C 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 unapproved use. 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 unapproved use, its comparators, the disease state, and how the unapproved use 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.

5.2C 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 AHRQ and PCORI, reports from ICER, and HTAs from recognized public or private organizations, including international bodies such as NICE and CADTH. Summarize the information that is relevant to the unapproved use.

5.3C 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.

5.4C OTHER ECONOMIC OR OUTCOMES EVIDENCE

Include published studies that result in economic evidence or other outcomes that do not fit in Section 3.0C, for example, pharmacoeconomic, modeling, health care

utilization, pharmacoequity, productivity studies, and 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.

5.5C EFFECT ON EQUITY

Phase III RCTs and cost-effectiveness analyses typically do not address barriers to the equitable use of the product for the unapproved use. Such barriers may include, but are not limited to, access to specialists, health disparities and social barriers, stigma, and the patient's ability to afford and utilize a medication. While health equity data for new interventions may initially be very limited, equity considerations often have implications for value assessment and should be discussed.

5.6C EFFECT ON QUALITY MEASURES

This section is to accommodate information and research where the unapproved use of 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, this section is not applicable.

5.7C 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' families and caregivers. If no information exists, this section is not applicable.

6.0C DOSSIER APPENDICES

The following information is valuable to HCDMs and should be included in Section 6.0C, when possible.

6.1C REFERENCES CONTAINED IN DOSSIERS

Include citations for all known published clinical and economic studies in the bibliography section. Reprints of relevant published studies should be available on request, and where possible, links should be provided to original sources if they are free.

6.2C ECONOMIC MODELS

Include economic models.

6.3C PRODUCT PRESCRIBING INFORMATION

Include the FDA-approved PI and instructions for use for the approved uses of the product.

6.4C PATIENT INFORMATION

Include any patient information, such as patient PIs and medication guides, for the approved uses of the product.

6.5C MATERIAL SAFETY DATA SHEET

Include or link to a Material Safety Data Sheet for the product.

6.6C APPENDICES SPECIFIC TO DTX PRODUCTS

Privacy and data security

Information related to privacy and security is required to be included in an AMCP dossier. Although the intended audience of the dossier is HCDMs who may lack the expertise needed to thoroughly evaluate the privacy and data security specifications for DTX products, a thorough evaluation of privacy and data security is required since this is essential to a comprehensive evaluation. Moreover, a review of privacy and safety may be performed prior to an evaluation of the clinical evidence by a P&T committee or body. If needed, HCDMs may seek additional expertise from data information technology/security experts, establish a DTX subcommittee, or have a separate group, such as an innovation center, assist with DTX evaluation. DTX manufacturers may work directly with HCDMs to integrate and implement DTX. Manufacturers may also provide relevant links to related information (i.e., privacy policies, terms of service).

Items to be addressed in a privacy and data security appendix include the following:

- Certifications (e.g., SOC 2, HITRUST, PCI DSS, ITIL, ISO 27001, CIPP)
- Data encryption: software supports SSL encryption
- Antivirus software
- Data protection security measures
- Security information and event management solutions (SIEM), web application firewalls (WAF), SECOPS monitoring, managed security providers (MSSPs), security orchestration automation and response platforms (SOAR)
- Data backup and recovery solutions
- Details on where data are stored
- Processes for secure disposal of information technology equipment and media
- Intrusion detection systems (IDS) or intrusion prevention systems (IPS) used.
- Parental restrictions for minors
- Data integrity

- Cybersecurity
- Data privacy processes
- Multifactor authentication
- Ransomware protection
- Other hack prevention methods

Engagement

Manufacturers may specify how they define engagement in an optional appendix. Due to the wide variety of DTX products 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 DTX products. If engagement measures were used in clinical trials or real-world evidence, they may be addressed in Section 3.0C or Section 5.0C.

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 health care professionals may also be included.

Appendix A Pre-Approval Information Exchange Guidance

AMCP has a well-established history of supporting appropriate PIE to provide opportunities for critical, early scientific dialogue regarding new treatments and new indications for existing treatments. As early as 2016 with the publication of the AMCP Format Version 4.0,⁷⁵ the AMCP Format has addressed this need. More recently, the AMCP Format Version 4.1¹⁰ provided detailed guidance for unapproved products and unapproved uses.

Today, many manufacturers have pursued PIE with HCDMs, using the AMCP Format, as well as other means such as with the use of PIE communication tools.⁷⁶ These tools support useful bi-directional communication. Two external milestones have provided additional support for pre-approval dialogue between manufacturers and HCDMs. First, in 2018, the FDA published guidance on appropriate communications between manufacturers and payers, including PIE.³ Second, the PIE Act was passed in December 2022, amending the Federal Food, Drug, and Cosmetic Act to provide explicit legal protection for manufacturers conveying certain information about products in development to HCDMs, including unapproved uses of approved products.^{4,77}

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 payer 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 communication tools as an 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 impact on organizational budgets. This may include products targeting a clinical area that previously did not have treatment options, chronic disease states with increasing prevalence, and 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. Manufacturers are encouraged to proactively engage with HCDMs in a timely fashion to support critical planning processes. The communication timeline could vary from 6 to 12 months prior to anticipated FDA approval, depending on product characteristics and potential budget impact.

Information included in PIE should include the following:

- 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
- Information relevant to patient access
 - 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. These interactions should be viewed holistically with regard to conveying the previously identified PIE concepts, and manufacturers should ensure that follow-up interactions with HCDMs are efficient in updating information previously provided.

Manufacturers should be mindful of prior communications with HCDMs and provide meaningful, timely updates as appropriate.

Appendix B Additional Terms and Definitions

Biosimilar: A biosimilar is a biological product that “is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and has “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”¹⁵

Budget Impact Models: A budget impact model estimates the expected changes in the expenditure of a health care system after the adoption of a new intervention in a payer-relevant time frame. Budget impact models provide a means of synthesizing available knowledge to estimate the likely financial consequences of adopting an intervention, typically from a payer perspective.

Care Pathways: Care pathways have been used widely in health care, and while definitions vary, care pathways are generally characterized as a method of patient care management that is based on clinical practice guidelines, with the objectives of improving quality of care, reducing variation in clinical practice, and improving the allocation of health care resources.⁷⁸

Comparative Effectiveness Research (CER): The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policymakers with making informed decisions that will improve health care at both the individual and population levels.⁷⁹

Companion Diagnostic Test (CDT): CDTs have been defined in various ways.

The FDA describes a CDT as one that provides information essential for the safe and effective use of a corresponding therapeutic product.²⁴ More generally, a CDT is defined as a test that provides information that improves the safety or effectiveness of a pharmaceutical or biologic. CDTs can be used to:

- Identify patients who are most likely to benefit from a particular therapeutic product.
- Identify patients likely to be at an increased risk for serious adverse reactions because of treatment with a therapeutic product.
- Monitor patient response to treatment for the purpose of adjusting the treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness.

CDTs (both in vitro diagnostic and medical imaging) may assess the presence of molecular biomarkers including the following forms:

- Genomic/epigenomic (deoxyribonucleic acid-based) biomarkers.
- Transcriptomic (ribonucleic acid-based) biomarkers.
- Proteomic (protein-based) biomarkers.
- Metabolomic (metabolite-based) biomarkers.

Cost-benefit Analysis: An analytical technique derived from economic theory that enumerates and compares the net costs of a health care intervention with the benefits that arise because of applying that intervention. For this technique, both the net costs and the benefits of the health intervention are expressed in monetary units.⁸⁰

Cost-consequence Analysis: An analytical technique that compares the health intervention of interest to one or more relevant alternatives, listing the cost components and various outcomes of each intervention separately. This type of economic analysis does not indicate the relative importance of the components listed and leaves it to the decision-maker to form their own view.⁸⁰

Cost-effectiveness Analysis: A systematic method of comparing two or more alternative programs by measuring the costs and consequences of each. A distinguishing feature of cost-effectiveness analysis is that the consequences (health outcomes) of all programs to be compared must be measured in the same common units—natural units related to the clinical objective of the programs (e.g., symptom-free days gained, cases prevented, quality of life-years gained).⁸⁰

Cost-minimization Analysis: A type of pharmacoeconomic analysis comparing two alternative therapies only in terms of costs because their outcomes (effectiveness and safety) are found to be or expected to be identical.⁸⁰

Cost-utility Analysis: A specific type of cost-effectiveness analysis that compares two or more alternative choices in terms of both their costs and outcomes, where the outcomes are measures of utility or preference, often as quality-adjusted life-years gained. Cost-utility analysis has been considered the standard methodology for evaluating the cost-effectiveness of health care choices.⁸⁰

Decision Analysis: A quantitative approach to decision-making under conditions of uncertainty in which all relevant elements of the decision—alternative actions, chance events (along with their probabilities of occurrence), and final consequences—are stated explicitly in a model. Multiple types of data can be incorporated from a variety of sources. This model typically takes the form of a decision tree or an influence diagram and permits the decision-maker to systematically determine the relative value of alternative courses of action.⁸⁰

Decision Tree: A schematic diagram depicting the logical structure of a choice under conditions of uncertainty, including all relevant alternative decisions available to the decision-maker as well as the values and probabilities of all relevant downstream consequences.⁸⁰

Digital Therapeutics: Health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has demonstrable positive therapeutic impact on a patient's health.^{54,81}

Effectiveness: The actual effects of treatment by the product under “real life” conditions (e.g., patients not always remembering to take their doses, physicians often prescribing doses less than the lowest FDA recommended dose, side effects not all controlled). Head-to-head effectiveness studies with similar products are preferable.

Efficacy: The *potential* effects of treatment by the product under optimal circumstances (e.g., patients all taking their doses at the right times, physicians prescribing FDA-recommended doses, side effects appropriately monitored). Efficacy studies are typically the foundation of product submissions to the FDA. Studies that compare the efficacy of therapeutic alternatives, rather than to placebo, are preferable.

Evidence-based Medicine: An approach to health care decision-making in which the decision-maker is aware of all the relevant evidence and its strengths and weaknesses and is then able to apply that knowledge to decisions. Evidence-based medicine, therefore, consists of clinical expertise and patient preferences combined with critical appraisal of clinical research, with the goal of providing optimal individual patient care. Optimal care thus considers patient outcomes and the relative efficiencies among competing alternatives, as demonstrated in the medical literature. This approach to patient care demands that the decision-maker's expertise and the appraisal of the clinical evidence base are up to date.⁸²

Evidence-based Medicine—Alternative Definition: The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

Formulary: A periodically updated list of medications and related products and therapies that includes information representing the clinical judgment of physicians, pharmacists, and other experts in the diagnosis and treatment of disease and promotion of health.

Formulary System: An ongoing process whereby a health care system, through its physicians, pharmacists, and other health care professionals, identifies and establishes policies on the use of drugs and related products and therapies that are the most medically appropriate and cost-effective to best serve the health interests of the patient populations it represents.

Health Economics: A discipline that analyzes the economic aspects of health and health care and that usually focuses on the costs (inputs) and the consequences (outputs) of health care interventions using methods and theories from economics and medicine.⁸⁰

Health-related Quality of Life: A broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, attitudes, values, perceived levels of satisfaction, and general well-being with respect to either specific health conditions or life from the individual's perspective. (See Patient-reported Outcomes.)⁸⁰

Incremental Cost-effectiveness Ratio (ICER): ICER is a common metric used to evaluate results of cost-effectiveness and cost-utility analyses. ICER is the difference in costs divided by the difference in outcomes between two comparators.⁸⁰

Interchangeable Biosimilar: The standard for “interchangeability” includes (1) biosimilarity to the reference product, (2) demonstration that the product “can be expected to produce the same clinical result as the reference product in any given patient,” and (3) proof that the risk in terms of safety or diminishing efficacy of alternating between the biosimilar and reference product is not greater than the risk of continuous use of the reference product. Interchangeable biosimilars may be substituted for the reference product without prescriber intervention, though differences in state laws limit the generalizability of automatic substitution.¹⁵

Markov Model: A complex health economics treatment model that describes the natural history of particular diseases, with or without treatment. To capture all critical events, Markov models can categorize health status with a higher level of detail and divide the model's time perspective into finer intervals than is possible with decision trees.⁸⁰

Model: In the context of health care evaluation, a model is an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs.⁸³

Modeling: The development of a simplified representation of a system (e.g., population). A particular model may be

analytical, visual, or both. In pharmacoeconomics specifically, or health economics in general, analytical models can be used to pose and answer questions about interventions that cannot be directly answered by clinical trials because of time and financial constraints.⁸⁰

Outcomes Research: The scientific discipline that evaluates the effect of health care interventions on patient-related, if not patient-specific, clinical, humanistic, and economic outcomes. Outcomes research is generally based on the conceptual framework that evaluation of treatment alternatives involves the simultaneous assessment of multiple types of outcomes that are disease related.⁸⁰

Patient-reported Outcomes: An umbrella term that includes outcome data reported directly by the patient. It is one source of data that may be used to describe a patient's condition and response to treatment. It includes such outcomes as global impressions, functional status, well-being, symptoms, health-related quality of life, satisfaction with treatment, and treatment adherence.⁸⁰

Pharmacoeconomics: The scientific discipline that assesses the overall value of pharmaceutical health care products, services, and programs. Of necessity, it addresses the clinical, humanistic, and economic aspects of health care interventions in the prevention, diagnosis, treatment, and management of disease. Pharmacoeconomics thus provides information critical to the optimal allocation of health care resources. The field encompasses experts in health economics, risk analysis, technology assessment, clinical evaluation, epidemiology, decision analysis, and health services research.⁸⁰

Pharmaco-equity: Ensuring that all individuals, regardless of race and ethnicity,⁸⁰ socioeconomic status, or availability of resources, have access to the highest-quality medical therapy required to manage their health needs.^{84,85}

Prescription Digital Therapeutics (PDTs): Product, device, internet application, or other technology that (1) is cleared or approved under section 510(k), 513(f)(2), or 515 of the Federal Food, Drug, and Cosmetic Act; (2) has a cleared or approved indication for the prevention, management, or treatment of a medical disease, condition, or disorder; (3) primarily uses software to achieve its intended result; and (4) is a device that is exempt from section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act under section 801.109 of title 21 of the Code of Federal Regulations (or any successor regulation).^{86,87}

Quality-adjusted Life-year (QALY): A universal health outcome measure applicable to all individuals and all diseases, thereby enabling comparisons across diseases and across programs. A QALY combines, in a single measure,

gains or losses in both quantity of life (mortality) and quality of life (morbidity).⁷²

Real-world Data: Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of real-world data include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as DHTs) that can inform on health status.⁸⁸

Real-world Evidence: The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data.⁸⁸

Rule of Rescue: A term applied to the ethical imperative to save individual lives regardless of the cost if rescue measures are available. Regarding the distribution of health care services, the rule of rescue supplements rather than substitutes for the evidence-based consideration of comparative cost-effectiveness. For example, Australia's Pharmaceutical Benefits Advisory Committee considers the rule of rescue a relevant factor when the cost-effectiveness level is unacceptable, along with the following:

- No alternative pharmacological or nonpharmacological intervention exists to treat patients with the identified condition.
- The defined condition must be severe, progressive, and expected to lead to premature death.
- The defined condition applies to only a very small number of patients.⁸⁹

Sensitivity Analysis: A way to analyze the effect of uncertainty in an economic analysis or a decision (see Decision Analysis and Modeling). The simplest form of sensitivity analysis is a one-way analysis where the value of one variable is changed while keeping the other variables constant, and the effect on results is evaluated.⁸⁰

Specialty Pharmaceuticals: There is no generally accepted definition of specialty pharmaceuticals; however, for purposes of the AMCP Format, a product may be considered a specialty pharmaceutical if it requires a difficult or unusual process of delivery to the patient (preparation, handling, storage, inventory, distribution, REMS programs, data collection, or administration) or patient management before or following administration (monitoring, disease, or therapeutic support systems).⁹⁰

Tornado Diagram: A set of one-way sensitivity analyses displayed in a single graph, with the most critical variable in terms of effect at the top of the graph and the rest ranked according to their effect thereafter, hence, the "tornado" or funnel appearance of the graph.⁸⁰

Appendix C Sample Unsolicited Request Letter

[Date]

Medical Information/Medical Communications Department [Name of Company]

[Address]

[City, State, Zip Code]

Dear [Name]:

[Organization name] has adopted the AMCP Format for Formulary Submissions detailing the process and evidentiary needs for the provision of clinical and economic information to support formulary consideration. Please consider this letter as an unsolicited request for an AMCP Format Product Dossier for your product [Name of Product or Products here]. Per the AMCP Format, the dossier should contain all available medical, economic, and other scientific information (including any unpublished or off-label study data that are to be considered by our organization) and pharmacoeconomic modeling on all comparator products that we consider for formulary inclusion or as part of therapeutic class reviews.

In addition, we request that you provide, for a period of 6 months, any new published or unpublished information on labeled or unlabeled uses that is specific to the information requested herein that may serve to further inform our decisions on the use of this product.

We consider this unsolicited request to represent the desired information to accompany a formulary submission. Manufacturers should submit a complete dossier well before they expect the product to be considered for formulary review. Our goal is to enable the [Organization Name] Pharmacy and Therapeutics Committee to make optimal evidence- and value-based decisions when selecting preferred treatment options. The AMCP Format describes a standardized template for manufacturers to construct and submit a formulary dossier. The dossier is designed to make the product evaluation process in formulary development more complete, evidence-based, and rational.

By submitting this request, we recognize that confidential information may be provided. We also recognize the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances.

If you require additional information, please call [XXXX].

Sincerely,

Appendix D Formulary Monograph Template

INDIVIDUAL PRODUCT REVIEW

Generic Name: [Name]

Brand Name: [Name]

Company: [Text]

Date of Review: [Month/Year] Reason for Review: [Text]

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Product Background

Review Methodology

Authorship

References

ABBREVIATIONS USED IN THIS MONOGRAPH

EXECUTIVE SUMMARY

Summary of Key Questions/Issues and Results of Investigation

[Text. The answers to key questions should be no more than a paragraph of modest length. If no evidence was found to answer a particular question, state “No evidence found.”]

Issue 1: What is the evidence of efficacy from clinical trials?

[Text]

Issue 2: Is there sufficient evidence to assess real-world comparative effectiveness?

[Text]

Issue 3: What is the evidence of safety?

[Text]

Issue 4: What is the value proposition for this product?

[Text]

Issue 5: Are there identifiable patient subgroups in which this treatment will be most cost-effective?

[Text]

RECOMMENDATIONS TO THE COMMITTEE

[Findings, key issues, and conclusions summarized as one or two short paragraphs that explain the logic leading to the recommendations.]

Therefore, the following Pharmacy and Therapeutics Committee action is recommended:

DISEASE BACKGROUND

DISEASE DESCRIPTION

[Text]

DISEASE BURDEN

[Text]

PATHOPHYSIOLOGY

[Text]

TREATMENT ALTERNATIVES

[Discussion of other existing pharmacologic alternatives or nonpharmacologic treatments that could be used in place of the drug being reviewed. If there are no existing treatment modalities, indicate “best supportive care” etc. and delete the next two subsections.]

Preferred Existing Therapy

[Discuss current treatment standards. If there is a “gold standard” treatment that is endorsed by practice guidelines or specialty society opinion statements, reference these authorities.]

Other Therapeutic Alternatives

[Discuss other generally accepted treatment options, including “watchful waiting” or “best supportive care” if these are considered appropriate.]

PRODUCT BACKGROUND

PHARMACOLOGY

[Brief description of mechanism. If it is a novel mechanism, a longer description may be appropriate.]

PHARMACODYNAMICS

[Text summary of relevant pharmacodynamic considerations]

PHARMACOKINETICS

[Text summary, if kinetics will factor significantly into the decision, including, but not limited to, absorption changes when administered (e.g., with food and medications), bioavailability, time to peak concentration, overall drug exposure, metabolism and clearance, multiple dosing, and elimination in patients with hepatic or renal impairment or who are taking interacting drugs)]

ADVERSE EVENT PROFILE

[Brief text summary of known side effects and general tolerability from the PI or other available sources. If clinically important, include a brief table of side effects from the PI, listing only side effects with incidence rates significantly different from placebo. This section is for discussion of routine side effects. Major safety issues should be discussed under Issue 3 above.]

DRUG INTERACTIONS

[List these from the PI. Include a table if appropriate.]

REVIEW METHODOLOGY

DATABASES SEARCHED

Medline

Embase

Cochrane Central Register of Controlled Trials

ClinicalTrials.gov

Other [Name]

SECONDARY SOURCES

Cochrane Database of Systematic Reviews

BCBSA TEC

NICE

Other [Name]

SEARCH STRATEGY

[Text]

INCLUSION CRITERIA

[Text]

SEARCH RESULTS

Study Type

Randomized controlled trials (RCT)

Meta-analyses of RCTs

Systematic reviews

Randomized pragmatic trials

Prospective cohort studies

Retrospective cohort or case-control studies

Economic modeling studies

Case series

RCT abstracts, not peer-reviewed

Other abstracts, posters, etc. not peer-reviewed

STUDIES/ARTICLES EXCLUDED FROM EVIDENCE SYNTHESIS

Study/Article Excluded	Reason for Exclusion

AUTHORSHIP

Review prepared by: [author's names, degrees, and organization].

REFERENCES

Include references, cited appropriately based on the organization's preferred style [e.g., American Psychological Association (APA), Modern Language Association (MLA)].

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