FORMAT 4.1

AMCP Format for Formulary Submissions

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

TABLE OF CONTENTS

ACKNOWLEDGMENTS

AMCP acknowledges the contributions of many individuals who have devoted substantial time, expertise, and commitment to the preparation of Version 4.1 of the AMCP Format for Formulary Submissions.

Contributors from the AMCP Format Executive Committee

2019–2020 Committee Members

James Daniel "Dan" Allen, BS Pharm, PharmD

Lisa Cashman, PharmD

Kevin Chang, PharmD

Cindy Giambrone, PharmD

Jennifer Graff, PharmD

James Hopsicker, RPh, MBA, Board Liaison

Alan D. Pannier, PharmD

Alex Peaslee, PharmD

Pete Penna, PharmD, Observer

Lauren Pusateri-Nilson, PharmD

Cynthia Reilly, MS, BS Pharm, AMCP Staff Liaison

Elizabeth Sampsel, PharmD, MBA, Observer

Kimberly Saverno, PhD, RPh

Iris Tam, PharmD, FAMCP, Chair

Patricia Thornewell, PharmD

John B. Watkins, BCPS

Ellen Whipple, BS Pharm, PharmD

T. Jeffrey White, PharmD

Stephanie Yu, PharmD

2018–2019 Committee Members

James Daniel "Dan" Allen, BS Pharm, PharmD

Steven G. Avey, MS, RPh

Mary Jo Carden, RPh, JD, AMCP Staff Liaison

Lisa Cashman, PharmD

Jennifer Graff, PharmD

Paul Jeffrey, PharmD, Board Liaison

Jeff Lee, PharmD

Vincent Lin, PharmD

Newell McElwee, Pharm, MSPH

Alan D. Pannier, PharmD

Pete Penna, PharmD

Elizabeth Sampsel, PharmD, MBA, Ex-Officio

Kimberly Saverno, PhD, RPh

Iris Tam, PharmD, FAMCP, Chair

Patricia Thornewell, PharmD

John B. Watkins, BCPS

T. Jeffrey White, PharmD

The AMCP Format 4.1 was updated by the AMCP Format Executive Committee. Work was initiated by the 2018–2019 Committee and completed by the 2019–2020 Committee. The update process included a public comment period during which time stakeholders from the manufacturer, payer, academia, consultancy, and professional association perspectives submitted comments. A representative from the U.S. Food and Drug Administration (FDA) also reviewed the draft and provided comments.

AMCP and the Format Executive Committee wishes to recognize Sean D. Sullivan, BScPharm, PhD, (Committee Chair for Versions 1.0, 2.0, 2.1, and 3.0) and Richard N. Fry, RPh, for their long-standing leadership and key contributions to previous versions of the AMCP Format.

PUBLISHER'S NOTE

AMCP is pleased to provide this resource to its members and other stakeholders. As with previous versions of the 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 (HCDMs). Development and use of dossiers is at the discretion of the manufacturer and is 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 for Formulary Submissions (the AMCP Format) has provided a framework to advise manufacturers regarding important health care decision maker (HCDM) evidence needs for evaluating 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 medical products for coverage or reimbursement.

In April 2016, the AMCP Format Version 4.0 incorporated updated considerations to foster rigorous, relevant, and ongoing scientific dialogue between manufacturers and HCDMs in assessing the safety, effectiveness, and value of new health technologies. Additional revisions at that time included considerations to correspond with the evolving health care environment, including incorporation of biosimilars, medical devices, comparative effectiveness research, companion diagnostic tests, and logistical guidance on developing and updating dossiers. The AMCP Format Version 4.0 also introduced the concept of providing evidence before approval by the U.S. Food and Drug Administration (FDA), and reinforced the need for ongoing communication between manufacturers and HCDMs.[3,4] The AMCP Format Executive Committee (FEC) 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]

HCDMs need and are interested in receiving information from manufacturers about unapproved products and about 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. Recent 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.

AMCP encourages the use of dossiers based on the AMCP Format Version 4.1 as a mechanism for manufacturers to communicate information about unapproved 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 guidance, FEC 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.

THE ROLE OF THE AMCP FORMAT

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

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, credible clinical and economic information needed by HCDMs.
- Recommending economic analyses and models to project the budgetary and cost impact on the HCDM's organization and its patient or member population as well as to assess the cost-effectiveness and economic value of a product (assessments of economic value apply only to Approved Product Dossiers).
- 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 analysis.

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 Executive 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 non-misleading way and that meets currently accepted standards for evidence-based medicine and health technology assessment. Likewise, it is the HCDM's responsibility to critically evaluate the evidence supplied according to currently accepted and published approaches to Pharmacy and Therapeutics Committee review processes and formulary decision-making best practices, which have been reported in the literature.[5-7] 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 dossiers, which are communicated to HCDMs only on unsolicited requests (reactive communication), because these dossiers contain information that extends beyond, and are sometimes inconsistent with, products' prescribing information/package insert or labeling (i.e., any and all off-label uses) approved by the U.S. Food and Drug Administration (FDA). The increasing need for HCDMs to begin to evaluate products before regulatory approval and market launch has long been a concern and recently been recognized by the FDA.[3] Now, the AMCP Format Version 4.1 expands its recommendations and provides guidance on the development and communication of dossiers for unapproved products and unapproved uses of approved products for which FDA approval is being sought, adding to the long-standing guidance for traditional dossiers for approved products. Thus, the AMCP Format has adopted the following terms: Unapproved Product Dossiers, Approved Product Dossiers, and Unapproved Use Dossiers.

GENERAL DEFINITIONS AND CONSIDERATIONS

This section defines certain key terms used throughout the AMCP Format for Formulary Submissions and provides 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 health care decision-makers (HCDMs) for the purpose of formulary, coverage, policy, and reimbursement decision-making.

In 2019, the AMCP Format Version 4.1 expanded its recommendations to provide guidance on the development and communication of dossiers for unapproved products, and unapproved uses of approved products for which U.S. Food and Drug Administration (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:

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.

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).

Unapproved Use Dossier

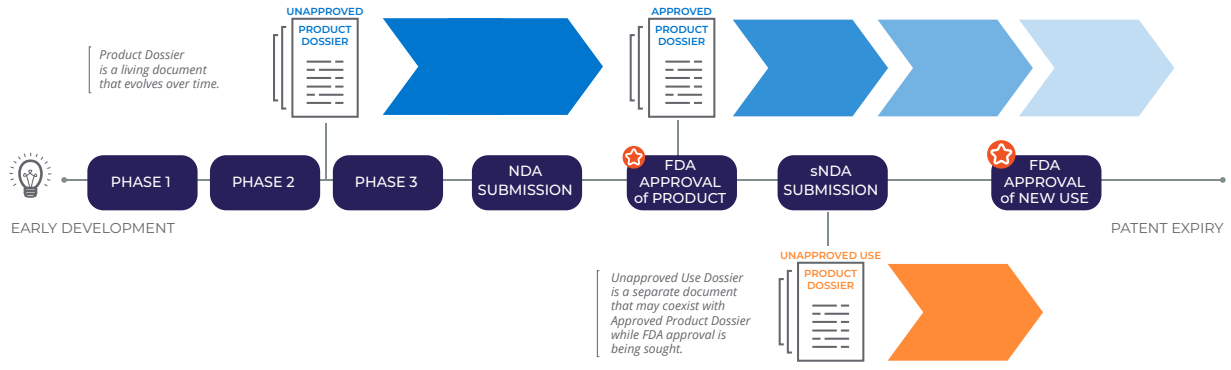
- Contains information about off-label uses for which the manufacturer is seeking FDA approval.
- Is used by manufacturers to communicate information to HCDMs about unapproved uses of an approved product for which the manufacturer is seeking FDA approval.

Product dossiers developed by manufacturers can be viewed as a living document that evolves and is continuously updated when new evidence and information becomes 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 continuously during the pre-approval period as evidence and information become available. At the time of FDA approval of the product, the manufacturer converts the Unapproved Product Dossier into an Approved Product Dossier and updates it throughout the post-approval period as more on-label and off-label evidence and information becomes available. An Unapproved Product Dossier and an Approved Product Dossier do not coexist during the product life cycle. That said, the Format Executive Committee (FEC) recognizes that the manufacturer may internally have two documents during the product's pre-approval period (e.g., the Unapproved Product Dossier for communication to HCDMs and a draft of the Approved Product Dossier being prepared for anticipated FDA approval). *See Figure 1.*

Subsequently, during the post-approval period, if the manufacturer chooses to develop a dossier for an unapproved use of the approved product for which FDA approval is being sought, a separate document may be developed for the manufacturer to communicate to HCDMs since the Unapproved Use Dossier discusses only the unapproved use for which the manufacturer is seeking FDA approval while the Approved Product Dossier includes evidence and information about any and all unapproved (off-label) uses that are supported by evidence.[3] Here, the FEC recognizes that the manufacturer may need to maintain two documents during the post-marketing period (e.g., the Approved Product Dossier containing all on- and off-label information and the Unapproved Use Dossier containing only the unapproved use for which FDA approval is being

Figure 1. AMCP Dossier Relative to Major Milestone Events of a Product's Life Cycle



NDA = New Drug Application
sNDA = Supplemental New Drug Application

For Illustrative purposes only. Timeline is not to scale.
Milestone events shown may vary and may not be all inclusive of a product's life cycle.
Manufacturer has discretion on the development of dossiers at all stages of life cycle.

sought). If there are multiple unapproved uses for which FDA approval is being sought, it is the manufacturer's discretion to include all unapproved uses in one Unapproved Use Dossier or develop separate 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.

In summary, an Unapproved Product Dossier is converted into the Approved Product Dossier at the time of FDA approval; during the post-marketing period, an Unapproved Use Dossier may be developed separately from the Approved Product Dossier if FDA approval is being sought for the unapproved use.

The evidence and information elements recommended in the AMCP Format are guidelines only; there is room for manufacturer discretion. It is fully understood that certain elements may not be provided by manufacturers for a variety of reasons (e.g., timing, availability, regulatory, legal, compliance, confidentiality, manufacturer discretion). The FEC strongly recommends that dossiers be updated with new, material information when available and communicated to HCDMs throughout the development of an unapproved product or unapproved use of an approved product until the time of FDA approval.

Creation and communication of dossiers by manufacturers must comply with current laws, regulations, and manufacturers' own policies, procedures, and compliance programs. At all times, manufacturers have discretion on whether to develop any dossiers. The development and communication of dossiers are at the discretion of manufacturers (e.g., a manufacturer may opt out of creating and providing dossiers to HCDMs).

Table 1 below summarizes key characteristics of each type of dossier. Readers should refer to the more detailed guidance on the evidentiary needs and recommendations about each type of dossier described later within the AMCP Format.

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 off-label 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 an unapproved use of an approved product for which FDA approval is being sought No characterizations/ conclusions should be made regarding the safety or effectiveness of the unapproved use

Continues.

	Unapproved Product Dossier	*Approved Product Dossier*	*Unapproved Use Dossier*
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 on-label and any/all off label information)	Used per the manufacturer's discretion to communicate information to HCDMs about unapproved uses of an approved product for which FDA approval is being sought
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	Yes, value that is grounded in clinical and economic evidence and information may 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 unapproved use
Why do HCDMs need a dossier?	To plan and budget for future coverage and reimbursement decisions about an unapproved product before FDA approval of the unapproved product	To evaluate an approved product for formulary, coverage, policy, or reimbursement decisions	To plan and budget for future coverage and reimbursement decisions about an unapproved use of an approved product before FDA approval of the unapproved use
When should the manufacturer have the dossier ready for HCDMs?	Any time before FDA approval of product; at the discretion of the manufacturer Typically, 6–12 months before FDA approval or up to 2+ years	Any time after FDA approval of the product; at the discretion of the manufacturer Typically, soon after FDA approval and availability of the product PI and price	Any time while the manufacturer is seeking FDA approval for the unapproved use of the approved product; at the discretion of the manufacturer Typically, based on a key milestone at the manufacturer's discretion
How should the manufacturer provide the dossier to HCDMs?	The manufacturer may provide the dossier based on their discretion and internal policies and procedures	On an unsolicited request only as the dossier contains on-label and any/all off-label information	The manufacturer may provide the dossier based on their discretion and internal policies and procedures
Who from the manufacturer should communicate or provide the dossier?	The FEC strongly recommends personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities	Personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities	The FEC strongly recommends personnel with appropriate medical/clinical/scientific credentials, expertise, and responsibilities

Continues.

	Unapproved Product Dossier	*Approved Product Dossier*	*Unapproved Use Dossier*
Who is the intended audience for the dossier?	HCDMs, payers, and entities that make or influence formulary, coverage, policy, and reimbursement decisions	HCDMs, payers, and entities that make or influence formulary, coverage, policy, and reimbursement decisions	HCDMs, payers, and entities that make or influence formulary, coverage, policy, and reimbursement decisions
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 off-label uses 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 or 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	Anticipated product price or reflected as a range The manufacturer has discretion on whether and how to provide economic information
When should the dossier be updated?	When new information becomes available; at the discretion of the manufacturer	When new information becomes available; at the discretion of the manufacturer	When new information becomes available; at the discretion of the manufacturer
Is the manufacturer mandated to develop the dossier?	HCDMs need and want the dossier, but development of Unapproved Product Dossiers is at the manufacturer's discretion	HCDMs need and want the dossier, but development of Approved Product Dossiers is at the manufacturer's discretion	HCDMs need and want the dossier, but development of Unapproved Use Dossiers is at the manufacturer's discretion

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

HEALTH CARE DECISION-MAKERS AND MANUFACTURERS

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, hospital systems, Pharmacy and Therapeutics (P&T) Committees, health technology assessment organizations, clinical practice guideline bodies, and other organized health care systems that make or influence population-based health care decisions.

The term "manufacturer" is used throughout this document to refer to ANY company that develops, manufactures, or markets drugs (brands, generics, biologics, biosimilars, vaccines), tests (companion diagnostic tests), or medical devices.

PRODUCT

The term "product" used throughout includes medical products such as pharmaceuticals, biologics, 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 tests (e.g., companion diagnostic tests) and medical devices (e.g., syringes, glucometers, wearable technology, digital apps) 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 medical product may be commercialized. These decision-making processes may include FDA approval, clearance, licensures, etc.

COMMUNICATION BETWEEN MANUFACTURERS AND HCDMS

Communication of Health Care Economic Information for Approved Products

Communication between HCDMs and manufacturers is strictly regulated by the FDA.[8] 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" (FDAMA Section 114).[4] In 2016, the 21st Century Cures Act Section 3037 expanded and modernized FDAMA Section 114 related to communication of HCEI.[9] The 2018 FDA Final Guidance (Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities) 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 21st Century Cures and the FDA Final Guidance, is subject to competent and reliable scientific evidence.

Communication of Approved Product Dossiers

The FDA Final Guidance does not affect or change manufacturers' ability to develop and communicate Approved Product Dossiers that are provided to HCDMs on 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 the AMCP Format calls for information in that type of dossier that may be inconsistent with a product's FDA-approved PI 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 manner in which manufacturers can respond to unsolicited requests for information about products.[10] 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 his/her 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 well before FDA approval.[3] As such, it is not uncommon for HCDMs to request information or a dossier 6 to 12 months and possibly up to 2+ years before FDA approval. Historically, it has been challenging for HCDMs to obtain, and manufacturers to communicate, such information. To address this need, in April 2016, AMCP released the AMCP Format Version 4.0 which, for the first time, outlined guidance for manufacturers' provision of information before FDA approval under the section Dossier Information Before FDA Approval.[11] Now, the AMCP Format Version 4.1 updates this guidance to describe the development and communication of Unapproved Product Dossiers and Unapproved Use Dossiers by manufacturers to HCDMs.

The AMCP Format Version 4.1 outlines the evidentiary needs for Unapproved Product Dossiers and Unapproved Use Dossiers; however, both HCDMs and manufacturers need to be cognizant that the availability of evidence and information at various 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.

The FEC 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 FEC 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.

Additional Considerations for Manufacturers

Given the complex regulatory and legal environment, manufacturers should consider and establish their own acceptable policies and procedures on developing and updating dossiers as well as communicating and disseminating dossiers, including the handling of requests. For example, consider policies and procedures to address (not exhaustive list): 1) What specifically constitutes a request for a dossier versus 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; 5) How to communicate Unapproved Product Dossiers and Unapproved Use Dossiers.

Bidirectional Communication of Information

Substantial ongoing and bidirectional, rather than unidirectional, communication and feedback between the HCDM and manufacturer throughout the product evaluation process is critical 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 into 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 should share 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 with manufacturers. 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 experience 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 up front. 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 management 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 such as medical personnel responsible for scientific information and scientific exchange as well as commercial personnel responsible for market access and contracting discussions.

As mentioned earlier, one can 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 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 to preserve the confidentiality of that information. We note that evidence dossiers submitted to government authorities in the United States, 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 that a confidentiality agreement was executed, if one was executed.

UPDATING DOSSIERS

Updating Dossiers for Approved Products

A common question from manufacturers is, "When should a dossier be updated?" The FEC 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 (not exhaustive):

- 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., established 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 should or should not receive 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 and less relevant 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 HCDMs 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., price increase, 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 only 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, the HCDM may, at the time of the original Approved Product Dossier request, include a statement that he/she 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 FEC recommends that the request for updated dossiers should not be indefinite and manufacturers should determine their own policies and procedures. Allowance for this process will avoid HCDMs from having to submit numerous requests for updated information, especially since they may not be aware when updated dossiers may be available. Additionally, 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 HCDMs 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 black box 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 indications 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 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 development or update, such as initiation of phase 3 trials, completion of phase 3 trials, application/submission for FDA approval, etc. AMCP and the FEC do not intend to prescribe specific time points or frequency of updates.

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 concise and clear as possible to streamline the evidence acquisition and review process. Manufacturers should NOT include overly verbose or superfluous content to meet page recommendations.

SUBMISSION OF DOSSIERS AND MODELS

Manufacturers should submit dossiers in an electronic format rather than in print. Electronic formats may include email, online platforms (e.g., AMCP eDossier System, 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 as a Microsoft Excel workbook or an alternative electronic format that is agreed upon by the requesting organization or its consultants and the manufacturer to facilitate ongoing dialogue as well as allow flexibility for user-defined analyses.

SPECIAL CONTENT CONSIDERATIONS

COMPARATIVE EFFECTIVENESS RESEARCH

While the AMCP Format for Formulary Submissions 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 by the U.S. Food and Drug Administration (FDA) of products is based on randomized controlled trials (RCTs) where the product is compared to placebo or, more preferably, a relevant, active comparator. Because of the highly controlled research setting, RCTs are considered the gold standard for clinical research with high internal validity and addresses the efficacy question, "Can it work?"

In contrast, CER conducted in a less controlled setting addresses the effectiveness question, "Does it work?" in the real world and relative to an active comparator. Real-world data from CER may not be available at the time of new product launch. However, in subsequent years, real-world CER may be conducted by the manufacturer as well as by other researchers, and the new evidence should be incorporated into the dossier. 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. Sometimes, it is just not feasible, for example, to conduct RCTs due to ethical or logistical factors.

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,[12,13] pragmatic clinical trials,[14,15] prospective observational studies,[16] retrospective observational studies,[17] systematic evidence reviews including indirect treatment comparisons and network meta-analyses,[18-21] and modeling studies.[22]

For assessing evidence from CER studies, the CER Collaborative (***www.cercollaborative.org***) — formed by AMCP, ISPOR , and National Pharmaceutical Council (NPC) — developed the CER Tool to assist health care decision-makers (HCDMs) in the evaluation and use of four types of outcomes research[23]: prospective and retrospective observational studies,[24] modeling studies,[25] and indirect treatment comparison studies.[26] HCDMs may also use tools to assess the body of evidence (e.g., Institute for Clinical and Economic Review (ICER) Evidence Rating Matrix,[27-29] Grading of Recommendations Assessment, Development and Evaluation (GRADE).[30-32]

DOSSIER 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 complexity of medical devices, it is recommended that medical devices that are most 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), health assessment devices and tests that elucidate health status, diagnosis, prognosis, etc. Medical device companies are encouraged to develop and make available medical device dossiers for HCDMs and health systems.

If a medical device company chooses to use the AMCP Format to create a device dossier, the company may indicate "not applicable" for recommendations 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.[33]

COMPANION DIAGNOSTIC TESTS

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.[34]

More specifically, in the AMCP Format, a CDT is defined as a laboratory test or assay that provides predictive and differential information about patients' responses to drug therapy. This contrasts with diagnostic or prognostic tests, which provide information about the disease process rather than response to treatment. Canestaro et al. developed the Companion test Assessment Tool (CAT) to assist HCDMs to determine whether a full technology review is necessary and, if so, what factors are likely to be most influential in the CDT's overall value.[35] The full publication provides a user-friendly, step-by-step algorithm and key questions to help HCDMs make these assessments.

There are other sources for background information regarding CDTs.[36-38] In addition, a number of other CDT evidence gathering and evaluating frameworks have been developed.[19,32,39-41]

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 order of preference):

- CDT codeveloped 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 manufacturer may or may not be the same as the CDT manufacturer/developer. In the case where the 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. This scenario may be important in understanding the ability of one company to adequately provide and communicate data and information related to another company's product. Obtaining evidence for CDTs is further complicated if the test is a laboratory-developed test developed by clinical laboratories and not reviewed, cleared, or approved by the FDA. 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 approaches for developing dossiers with CDT evidence:

- The CDT is codeveloped with the 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.

Despite this guidance, some CDT companies may not develop dossiers and obtaining scientific and clinical information may be difficult.

BIOSIMILARS

For FDA-approved biosimilars, HCDMs require a body of efficacy, safety, economic, and comparative effectiveness data like that of the innovator product to make rational, evidence-based decisions regarding coverage and reimbursement. Companies that produce biosimilars should develop and provide product dossiers like those of the innovator products.

A biosimilar has been 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."[42]

The FDA has provided guidance on the analyses and testing that will be enough to demonstrate biosimilarity and interchangeability. Companies that develop biosimilars should incorporate these considerations into the dossier 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 innovator product, biosimilar companies must clearly document whether clinical trials and other studies (e.g., pharmacokinetic studies, animal studies) were conducted with the innovator product or the biosimilar product. HCDMs should be able to distinguish whether biosimilars are supported by direct or extrapolated evidence. Requirements for biosimilars continue to emerge. 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.[42] Additional information on FDA guidance related to biosimilars may be found here:

- Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry. May 2019.[43]
- Biologics Price Competition and Innovation Act of 2009 (BPCI Act).[44]
- Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. April 2015.[45]
- Guidance for Industry: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry. April 2019.[46]
- Nonproprietary Naming of Biological Products: Update Guidance for Industry. March 2019.[47]
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the Public Health Service Act. Draft Guidance. August 2014.[48]
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Draft Guidance. December 2016.[49]
- Questions and Answers on Biosimilar Development and the BPCI Act. December 2018.[42]
- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (revision 2). December 2018.[50]

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."[51] Response, whether beneficial or adverse, to a treatment 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. Identification of heterogeneity should be noted in Section 2.2.2B(4) and the evidence and studies to support it be summarized in Section 3.0B or 5.0B, as appropriate. Readers are referred to additional information on heterogeneity of treatment effect.[52-55]

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

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.

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

As opposed to an Approved Product Dossier, there is no Executive Summary in an Unapproved 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 and because no characterization or conclusions should be made regarding the safety or effectiveness of the unapproved product.

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.

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
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)
NDA/BLA 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
PDUFA or FDA approval date	List the date or time frame (e.g., 2023, Q1'22) of anticipated FDA approval
Product launch data	List the date of anticipated product launch in the market

Continues.

Type of Information	*Description of Information*
Approval dates in other countries (outside of the United States)	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 completed, 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 completed, 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
Prevalence of condition associated with anticipated indication in the United States	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 United States	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: [ ] ≥$1,000,000 [ ] $500,000 to $999,999 [ ] $300,000 to $499,999 [ ] $100,000 to $299,999 [ ] $50,000 to $99,999 [ ] $10,000 to $49,999 [ ] ≤$9,999 Alternatively, or in addition, indicate any other information that might help HCDMs consider the anticipated cost impact of 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; PDUFA = Prescription Drug User Fee Act.

2.0A PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1A PRODUCT DESCRIPTION

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

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

Manufacturers are encouraged to provide as much detailed information about the unapproved product as possible. 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[1]; AMCP Format recommendation[2]):

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.[1]
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).[1]
3. Product information (e.g., drug class, device description, features).[1]
    - Generic, brand, chemical, or other given name of the unapproved product.[2]
    - Therapeutic class or category; American Hospital Formulary Service (AHFS) or other drug classification.[2]
    - Proposed mechanism of action.[2]
    - Pharmacology, pharmacokinetic, pharmacodynamic information.[2]
    - Drug/drug, drug/food, drug/disease interactions.[2]
    - Dosing and administration information (usually from clinical trials).[2]
    - Anticipated access and distribution information.[2]

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 subjects enrolled, subject enrollment criteria, subject demographics).[1]
5. Anticipated timeline for possible commercialization (e.g., FDA approval/clearance/licensure of the unapproved product).[1]
    - Date of new drug application (NDA), BLA, device premarket approval (PMA), 510(k) submission for FDA clearance.[2]
    - Date of FDA advisory committee review, if any.[2]
    - Date of anticipated FDA approval/clearance/licensure.[2]
6. Product pricing information.[1]
    - See Section 4.0A.[2]
    - Information may be provided here and/or in Section 4.0A.[2]
7. Patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).[1]
8. Product-related programs or services (e.g., patient support programs).[1]
9. 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 product).[1]
    - See Section 3.0A.[2]
    - Information may be provided here and/or in Section 3.0A.[2]
10. Other factual information per the manufacturer's discretion.2

2.2A DISEASE DESCRIPTION

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

It is understood that the exact indication of an unapproved 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 unapproved product. That said, HCDMs need to know basic disease-related information when reviewing information about unapproved products.

Manufacturers are requested to provide as much information as possible about the medical condition or disease state for which the unapproved product is being studied and FDA approval is being sought without making characterizations or conclusions about the safety or effectiveness of the product. 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, pathology, 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 product 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 the medical literature. Other sources may be used per manufacturers' discretion. Cite and reference all information.

3.0A CLINICAL EVIDENCE

Section 3.0A should consist of all clinical studies that support the unapproved product, reported in a clear and concise format.

Manufacturers should provide factual presentations of results from studies, including clinical studies of the unapproved product or bench tests that describe unapproved product performance. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product. Manufacturers should describe material aspects of study design and methodology and disclose material limitations related to the study design, methodology, and results. Manufacturers should also ensure that information and results are not selectively presented (e.g., both positive and negative or null findings should be presented).

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.

Typical information may include, but is not limited to phase 1, 2, and 3 studies (e.g., peer-reviewed publications; medical congress abstracts, posters, presentations) information from Clinicaltrials.gov; pre-clinical studies; data on file per manufacturers' discretion.

Manufacturers may use discretion to provide information in the form of study summaries only or evidence tables only or both.

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, 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., intended 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.
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 <one page (maximum two) for each study. Evidence tables should include the following items where available and applicable:

1. Citation (if unpublished, "data on file"), Clinicaltrials.gov ID number.
2. Treatments, sample size, length of follow-up.
3. Study design, inclusion and exclusion criteria.
4. Primary and secondary endpoints, results (when available).

4.0A ECONOMIC INFORMATION

AMCP and the Format Executive Committee (FEC) acknowledge that the price of a product is not disclosed until final approval by the FDA or market launch of the product. The FDA recognizes that HCDMs (payers, formulary committees, and other similar entities) need and are interested in receiving information from manufacturers about products that are not yet approved for any use. HCDMs need such information to begin to inform their plans and budgets for future coverage or reimbursement decisions well before FDA approval. A key piece of information is product pricing.[3]

The topic of pricing information was discussed at the FEC at great length and intensity as price is a controversial issue. It is not typical for manufacturers to disclose pricing information before product FDA approval, and many manufacturers may resist or refuse to disclose any pricing information before product FDA approval.

The FEC 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 before 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 an absolute dollar figure.

It is recognized that budget impact models and cost-effective models may not be feasible to construct or communicate before FDA approval because such models rely on certain outcomes and assumptions regarding effectiveness and safety of the 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 manner that is protected.

Information related to the economics surrounding an unapproved product may be provided in a variety of ways, which may include:

- 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.

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 – Economic 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 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 prescribed 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 its anticipated effects on the clinical evidence, health outcomes, and the economic consequences for the health care system. 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.

1.1B CLINICAL BENEFITS

Begin with the indication approved by the U.S. Food and Drug Administration (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:

1. Efficacy and effectiveness.
2. Comparative effectiveness relative to available alternative therapies.
3. Safety/tolerability.
4. Shortcomings of current 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:

1. Cost per unit.
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 (such as 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 to 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 DESCRIPTION

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

Manufacturers should provide detailed information about their product.

The product description consists of information that traditionally has been found in the FDA-approved label or prescribing information/package insert (PI) as described below. It can also contain information that goes beyond the scope of the PI.

Basic product information should be provided, including a brief discussion of what the product is, and any significant attributes that define the product's place in therapy (e.g., kinetics, adverse event profile). Verbatim language from the PI does not need to be supplied here. If there are no substantive data and information that can be provided beyond the PI, these sections should be left blank and the reader referred to the copy of the PI in the Appendix. In those cases where one or more of these attributes (pharmacology, pharmacokinetics, pharmacodynamics, contraindications, warnings, precautions, adverse events, interactions, and dosing) is of major significance in defining the value of a product, additional information beyond the PI should be provided.

The following are the components that should be supplied:

1. Generic, brand name, and therapeutic class of the product.
2. All dosage forms, including strengths and package sizes.
3. The National Drug Code number for all formulations. For specialty pharmaceuticals that may be covered under the medical or pharmacy benefit, additional codes are required in this section. Provide Healthcare Common Procedure Coding System codes applicable to these products, as well as any Current Procedural Terminology codes that are relevant to reimbursement. *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) and ICD-9-CM codes are also advisable to include for any indications specified in the PI. Inclusion of ICD-9-CM is to allow retrospective review of claims that contain ICD-9-CM since conversion to ICD-10-CM occurred in October 2015.
4. The average sales price (ASP) and wholesale acquisition (WAC) cost per unit size.
5. American Hospital Formulary Service (AHFS) or other drug classification.

6. FDA-approved indications and the date approval was granted (or is expected to be granted). Also, other significant off-label uses, and potential new indications being studied. It may be helpful to include hyperlinks to the relevant off-label sections within the dossier, as well as hyperlinks to Clinicaltrials.gov for the new indication studies.
7. Pharmacology.
8. Pharmacokinetics/pharmacodynamics.
9. Contraindications/warnings/precautions/adverse effects.
10. Special populations (e.g., pregnancy, pediatric use, renal impairment).
11. Interactions with suggestions on how to avoid them.
    - Drug/drug.
    - Drug/food.
    - Drug/disease.
12. Dosing and administration.
    - For specialty pharmaceuticals, include any instructions for preparation, administration, and a description of any unique type of delivery devices that do not appear in the package insert, as well as information on setting of care. Verbatim language from the package insert should not be supplied here.
13. Access (e.g., restrictions on distribution, supply limitations, anticipated shortages, and prescribing restrictions).
    - For a specialty pharmaceutical, this section should be expanded to cover the following information: considerations for the product around its distribution channels; prescribing restrictions for the product if applicable; handling instructions; ordering instructions for the product; patient access/assistance contact information.
14. Coprescribed/concomitant therapies, including dosages, recommended use of other agents or treatments with the product, and the rationale and clinical benefit associated with them. It may be helpful to refer to the PI when determining which therapies would be coprescribed/used concomitantly.
15. Describe how the product may affect quality measures (e.g., Healthcare Effectiveness Data and Information Set (HEDIS) scores, 30-day readmissions, Centers for Medicare & Medicaid Services star rating). Include studies that support this information in Section 3.0B.

2.1.1B PRODUCT COMPARISON

Concise comparison of PI information with the primary comparator products in the same therapeutic area focused on safety and efficacy and include dosing, indications, pharmacokinetic/pharmacologic profile, adverse effects, warnings, contraindications, interactions, and other relevant characteristics (expand as appropriate for the therapeutic class). The material may include a discussion of comparator products or services that the proposed product is expected to substitute for or replace. This information should be presented in tables. If direct head-to-head trials have been conducted on the product and its comparators, this should be noted here, and the reader referred to the review of those trials in Section 3.0B of the dossier.

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

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 comparator table.

2.2B PLACE OF THE PRODUCT IN THERAPY

The recommended length of Section 2.2B is 10 pages (maximum 15) for each indication.

Information presented in this section should be brief. Ideally, information should be provided in a table or bulleted list or another easy-to-read format. For products with multiple indications, the following information should be provided for each indication. Do not duplicate information presented in Sections 3.0B, 4.0B, and 5.0B.

2.2.1B DISEASE DESCRIPTION

The intent is to give the reader a good overall sense of the disease. The disease description should be brief and should include the disease and characteristics of the patients who are treated for the condition. 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. Present a brief summary of information from the literature for each topic.

Disease-specific descriptive information may include, but not be limited to:

1. Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product.
2. Pathophysiology.
3. Clinical presentation.
4. Societal, humanistic, and economic burden.

This section may be expanded to provide greater detail for some drugs 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 drugs 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 drugs 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: How is the disease/condition currently treated? How does the new product fit into standard or existing therapy?

Provide a summary of information from the literature for each topic; do not duplicate information included in other sections:

1. Summarize current approaches to treatment including principal therapeutic options (drug and nondrug), common practice patterns, or standards of care; briefly include recommendations supported by well-accepted or nationally recognized clinical practice guidelines and consensus statements; summarize details of these sources in Section 5.0B.

2. Describe the place and anticipated uses of the proposed product for treating disease, especially for certain subpopulations that can be targeted for the use of the product.

3. Indicate the appropriate care settings for the product such as self-administration by the patient, in the home by a health care professional, in an infusion therapy clinic, in a physician office, or in a hospital.

4. Describe heterogeneity of treatment effect, if any, related to the use of the product. Response to therapy may vary from patient to patient. Any information that substantiates heterogeneity effects (benefit and harms) of the proposed therapy should be described here and supported with evidence from studies in Section 3.0B (e.g., crossover study designs, N-of-1 studies, subgroup analyses).

5. Include proposed ancillary disease or care management intervention strategies provided by the manufacturer that are intended to accompany the product at launch. Services intended to accompany a specialty pharmaceutical at launch should be described. These may include any of the following: patient education services, nursing administration support services, programs intended to promote adherence, coordination of information among providers or facilities, sharps disposal, and financial assistance to patients. Specific claims made regarding the benefits of these services should be documented in this section and supported by scientific evidence described in this section or reported in Section 3.0B or 5.0B if applicable. It should be clearly stated when there is no scientific evidence to support claims of benefits for these services. For patient assistance programs, it is optimal to include the terms of the program and the expected number of beneficiaries.

6. Describe other product development or post-marketing obligations as required by the FDA such as a REMS, phase 4 trial, patient registry, restricted distribution channel, and other elements designed to assure the safe use of the product. In addition to the existing instructions for this section, if a multifaceted program intended to accompany the product at launch will include REMS alongside other elements, describe it in section 2.2.2B(5) and note in 2.2.2B(6) that the program contains a REMS component.

7. Describe ongoing post-approval monitoring of drug safety and adverse events. Ongoing post-approval monitoring and cost of adverse events for newly approved drugs should be conducted and included, if available or if applicable. Signals of adverse events indicating disproportional rates of events should be reported. The estimated cost of adverse events, including the cost of monitoring, hospitalizations, emergency room visits, and any other relevant costs associated with treating the adverse event should be included. In addition, the health care decision-maker should contact the drug company for current additional information related to drug safety and adverse events.

8. Describe the expected outcomes of therapy (e.g., a cure, palliation, relief of symptoms, quality of life, patient-reported outcomes, productivity). Describe any clinical markers that that are linked to disease outcome (e.g., low-density lipoprotein lowering).

9. Other key assumptions and their rationale.

2.3B EVIDENCE FOR COMPANION DIAGNOSTIC TESTS[56]

Drug Dossier with Companion Diagnostic Test

When a companion diagnostic test (CDT) has been codeveloped with a drug, or when the CDT is required per FDA labeling, then the four elements — 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 Section 2.3.1B and Section 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 Section 2.3.1B, Section 2.3.2B, and Section 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.

2.3.1B PRODUCT INFORMATION FOR CDT

The recommended length of Section 2.3.1B is five pages (maximum 10).

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).

3. Target: describe test target (e.g., biomarker, microarray patter).
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., diagnosis, prognosis and management, risk management, treatment, monitoring, or pre-symptomatic testing).
7. Indication and target populations; prevalence of disease/condition and CDT variant in target population.
8. Place of CDT in drug therapy.
9. Contraindications, warnings/precautions, 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 ACCE framework:
    - Analytical validity: How well does the test identify the target or marker 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 that tests positive have the medical condition?
        - Negative predictive value: How often does a patient that 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 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 progressions, risk-benefit assessment, morbidity, quality of life, 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 usual care, 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, price.
15. Copy of the product label or package insert.

2.3.2B PLACE OF CDT 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, health technology assessments (HTAs), 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 (randomized trials, prospective effectiveness trials, case series, retrospective studies, systematic reviews, meta-analyses).
4. Outcomes studies (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:

1. Setting and location of study.
2. Study design, research question(s)
3. Inclusion and exclusion criteria.
4. Patient characteristics (demographics, number studied, disease severity, comorbidities).
5. Intervention and control group.
6. Patient follow-up procedures (e.g., if an intention-to-treat [ITT] design is used, were drop-outs followed and for what time period?), 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 all clinical studies that support the use and value of the product reported in a clear and concise format. Specifically, the types of studies that should be included in this section are:

1. Prospective clinical studies that investigate any aspect of the product in patients regardless of study design. This includes randomized clinical trials, prospective observational studies, registries, and any other studies that measure clinical endpoints, patient outcomes, or collect information directly from patients. Study results and outcomes include efficacy, effectiveness, comparative efficacy, comparative effectiveness, safety, tolerability, long-term safety, patient preference, patient adherence, patient-reported outcomes, quality of life, evidence that identifies patient subgroups or clinical settings that may be more appropriate, and other clinically related outcomes.
2. Retrospective studies 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, or other novel sources of data.
3. Studies that synthesize the studies in #1 and #2 above such as indirect treatment comparisons and meta-analyses of the product and the primary comparators.

Information that may be listed in Section 5.0B includes the use and value of the product from other sources such as clinical practice guidelines, clinical pathways, previous reviews of product value by HTA agencies, and published systematic reviews by outside academic groups such as the Cochrane Collaborative.

Comparative evidence is a necessary component of a comprehensive product dossier, regardless of the methodology used to generate the evidence. For this reason, it is strongly recommended that studies involving CER be incorporated into the product dossier. Health care decision-makers (HCDMs) are particularly interested in head-to-head clinical studies between the proposed product and the principal comparators. Summaries of trials for key comparator products are desirable but not required.

In addition, clinical evidence that is relevant for this section includes the following:

- FDA-approved indications and unapproved uses.

  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 (e.g., organize and report on-label indications and information first and off-label thereafter). If data on 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.

- Published and unpublished studies and data.

  Studies available from published journals; medical congress abstracts, posters, and presentations (only when full publications are not available); information from manuscripts submitted or accepted by medical journals, Clinicaltrials.gov, press releases, manufacturers' data on file.

- Any study designs.

  Specific study designs are not prescribed in this section. Manufacturers should include studies that generate evidence about clinical outcomes which may include, RCTs (phase 2, 3, 4), open-label studies, pragmatic trials, observational or cohort studies, registries, and studies that use adaptive trial designs. See FDA guidance for adaptive trial designs.[57,58]

- Studies with one or more study arms.
- Study results regardless of positive, negative, or null findings.
- Studies inside and outside of the United States.
- Data and findings from the FDA and other U.S. governmental agencies.
- Ongoing clinical trials and links to their registry information.
- 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.

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

1. Large key studies that are critical or add significantly to the knowledge base of the product should be included as study summaries and evidence tables.

2. Smaller but informative studies that may add to the evidence base, but are not quite as rigorous as those listed above, should be included as evidence tables only.

3. 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 manufacturer may also 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. However, the manufacturer should disclose that certain studies have been excluded and describe the reasons for the exclusion via literature search strategy and/or Consolidated Standards for Reporting of Trials (CONSORT) diagram. Considerations for establishing inclusion or exclusion criteria may include, but are not limited to: study phase (phase 3 vs. phase 2 vs. phase 1), study design (e.g., controlled trial vs. case series), number of subjects (e.g., studies with greater than X number of subjects).

The manufacturer must clearly explain the objective rationale for delineation and assignment of studies into each of the categories above to avoid cherry-picking and bias. Since these definitions may vary depending on the context of the product, clinical setting, available treatment alternatives (e.g., common disorder vs. orphan disease), the manufacturer must justify how studies are included (study summaries vs. evidence tables vs. bibliography).

If the results of a trial have been reported in more than one journal article or conference abstract, poster, or oral presentation, all may be combined into one summary and one row of an evidence table, citing all the sources from which data have been drawn and clearly stating the total number of subjects. Discuss important study findings and comment on their implications for different patient populations. Systematic reviews or meta-analyses are to be included in Section 5.0B.

For products with more than one approved indication, the pharmaceutical manufacturer should decide how reports for on-label studies 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.

The length and level of detail for study summaries and evidence tables may vary based on the amount of available data. It must be noted that HCDMs want concise, focused, and user-friendly presentation of data. One of the most common complaints from HCDMs is that dossiers are too long.

The manufacturer should provide specific journal reprints, copies of congress abstracts, posters, and presentations, and other available study information on request by HCDMs. All reprint requests may be subject to the Physician Payments Sunshine Act (passed under the Affordable Care Act).[59]

For pharmaceuticals designated by the FDA as “breakthrough drugs” the evidentiary reporting requirements are the same as for other drugs. For biosimilars, basic evidentiary needs are the same as for “traditional” and “specialty” pharmaceuticals. While it is recognized that trials dealing with interchangeability, dosing equivalency, comparison with innovator agents, etc. are especially important, all trials dealing with biosimilars should be reported since there is often limited data available for such products, and formulary decision-makers need access to all relevant evidence and data.

3.1B 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, 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, 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 <one page (maximum two) for each study.

Evidence tables should include the following data elements:

1. Citation, (if unpublished, give abstract information or indicate “data on file”).
2. Treatments.
3. Sample size and length of follow-up.
4. Inclusion and exclusion criteria.
5. Design.
6. Primary endpoints.
7. Secondary endpoints.

8. 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.

9. Statistical significance.

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 tradeoff 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. 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 reflective of plan populations.

5. Safety data may be limited or from disparate sources.

6. Health care cost effects may not be generalizable across HCDMs.

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.

Decision-analytic based, cost-effectiveness models 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:

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 and endpoints to reflect clinical reality.

4.1.2B TYPES OF MODELS

There are several types of models that can be helpful for 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. There are several specific types of cost-effectiveness models, which are discussed in the Methods section below. 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 International Society for Pharmacoeconomics and Outcomes Research ISPOR and the Society for Medical Decision Making (SMDM) Modeling Good Research Practices Task Force.[22,60-65]

Budget Impact Models

Budget impact analyses address the question, "Is the technology affordable?" A budget impact model estimates "the expected changes in the expenditure of a health care system after the adoption of a new intervention."[66] Budget impact models are not intended to establish the overall value of health care technologies because they do not include the full effect 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 per-member per-month costs. Budget impact models use clinical data and can be relatively complex, and thus should follow the recommendations in this section and best practices published by ISPOR.[66,67]

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, copayment, 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.[22,60-65] 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 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. All assumptions should be clearly presented.
7. Specialty pharmaceuticals 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).
8. 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.
9. When possible, a standalone, 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 their health system or health plan.
10. Lastly, users of this document should recognize the AMCP Format is a set of recommendations on the types of evidence and reporting formats that are likely to be useful for HCDM. We recognize the need for flexibility, 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.[22,60-65]

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, including the economic impact of adverse events.
4. Outcomes of therapy for each clinical pathway.
5. Incremental cost and outcomes analysis presented in cost/consequences tables and as cost-effectiveness ratios.

Analytic Framework

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

Modeling Technique

There are several decision-analytic based approaches to constructing disease-based cost-effectiveness models, primarily: 1) decision trees, 2) Markov (cohort) models, and 3) patient-level simulation (discrete event simulation). There are advantages and disadvantages to each technique, mainly related to the conflicting factors of transparency and data availability versus the complexity of many diseases and their treatments. It is recommended that the simplest feasible modeling approach be used. In other words, the model should be sophisticated enough to capture the key aspects of the disease and treatments yet be well supported by high-quality data that are available to and interpretable by the user.

Perspective and Time Frame

The HCDM perspective is recommended for the primary analysis, with optional perspectives (e.g., societal, employer) conducted as secondary evaluations. The model should consider a time horizon that is appropriate to the disease being studied and reflect the decision-making and financial and budget constraints consistent with the perspective. The time horizon should be long enough to reflect all important differences in costs and outcomes between the technologies being compared. Adjustment for time preference should be incorporated as appropriate and follow U.S. Public Health Service Panel recommendations (discounting both future costs and health effects).[68]

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. If appropriate, these data should also be incorporated into the model.

Drug Safety Data

Clinically relevant adverse events observed in RCTs should be included in the model, as well as safety signals derived from appropriate observational studies. The economic impact of treatment-related adverse events should be incorporated into cost-effectiveness analyses. A wide range of estimates should be explored given the challenge of accurately ascertaining the likelihood of low-probability events.

Economic Data

Unit costs data ideally would be relevant to the decision-maker, based on health care system data. If specific health care system data are not available, costs from representative U.S. private payers, Medicare, and others may be used. Because the costs of infused and injected drugs may also depend on the site of care, models should take these attributes into consideration. Decision-analytic models should be sufficiently flexible to adapt the input assumptions to conform to local practice and billing patterns.

Utilities

Preference estimates should be derived from studies surveying either patients or the general population, using a direct elicitation method or an instrument such as the time tradeoff, standard gamble, EuroQol (EQ-5D), Health Utilities Index (HUI), Short Form-Six Dimension (SF-6D), or Quality of Well-Being (QWB). Because cost-effectiveness analysis is conducted at the population level, the ideal source of utility values is the general population. This may be impractical in some situations and trial-derived utilities may be used.

Demographic and Practice Pattern Data

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

Surrogate Markers

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

Expert Opinion

Data derived from expert panels are not generally acceptable, especially for key effectiveness or safety variables. However, this approach may be reasonable for other variables where estimates are not available through literature, databases, trials, or other typical sources. In such cases, the expert assumptions should be clearly stated and thoroughly tested in sensitivity analyses. Inputs obtained from an expert panel should be modifiable in case local opinion leaders disagree with the panel members.

Efficacy Versus Effectiveness

When feasible and scientifically plausible, efficacy results from RCTs should be transformed into effectiveness parameters. For example, this may involve inclusion of an adherence parameter into the model based on observational data. Documentation and clear description of the methodology will be necessary for health care system staff to evaluate the validity of this approach.

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 tradeoffs 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 seek input from clinicians to ensure that models have good face validity for the disease or condition being evaluated.

Both univariate and probabilistic sensitivity analyses should be conducted to provide a more complete picture regarding the robustness of the results. Analysts should justify the distribution used for each parameter that is included in a probabilistic sensitivity analysis. Comprehensive one-way sensitivity analysis of all parameters in the model is also strongly recommended, including assessment of effects on both incremental effectiveness (e.g., QALYs) and cost-effectiveness. However, the use of arbitrary lower and upper values is strongly discouraged. 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 sensitive parameters. The three to five parameters and two to three 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.[66,67]

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 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 or Medicare 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 and the total budget impact on the health system.

Sensitivity Analysis

Sensitivity analyses are recommended for assessing the uncertainty associated with the budget impact model. For assessing both structural and parameter uncertainty associated with the budget impact model, a variety of scenario analyses are recommended.

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 sensitivity 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.[61] 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 nonhealth economist to comprehend the analysis. The information and references should be accessible both 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 the format: 1) Introduction/Background, 2) Methods, 3) Results, 4) Limitations, 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 of 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 and QALY estimates.
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.[69] 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 a) is familiar with them, and b) agrees with the manufacturer to their use. Custom software models are generally discouraged but may be feasible 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 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, gender, 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 significantly 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 studies.

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

5.1B 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 specific to the product, its comparators, and the disease state and how the new product is anticipated to be included in or influenced by the guidelines. Summarize information from clinical practice guidelines briefly and, if feasible, provide a copy of the full guidelines on request or provide links to the original guidelines. The manufacturer should describe how it included or excluded clinical practice guidelines in this section.

5.2B 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 the Agency for Healthcare Research and Quality (AHRQ), the Patient-Centered Outcomes Research Institute (PCORI), reports from the Institute for Clinical and Economic Review (ICER), and HTAs from recognized public or private organizations, including international bodies such as National Institute of Clinical Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH). Summarize the information that is relevant to the product.

5.3B 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, and productivity studies. Conduct and reporting of studies in this section should follow accepted practice as evidenced by published methodology and reporting guidelines from reputable professional societies or government agencies. A description of how studies were selected for inclusion should be summarized and included.

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

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

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

5.5B EFFECT ON QUALITY

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

5.6B OTHER EVIDENCE OR INFORMATION

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

6.0B DOSSIER APPENDICES

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, provide a link to original sources if they are free.

6.2B ECONOMIC MODELS

Include economic models.

6.3B PRODUCT PRESCRIBING INFORMATION

Include FDA-approved label, PI, or prescribing information.

6.4B PATIENT INFORMATION

Include any patient information such as patient PIs.

6.5B MATERIAL SAFETY DATA SHEET

Include Material Safety Data Sheet for product.

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 Information

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 U.S. Food and Drug Administration.

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.

As opposed to an Approved 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 and no characterization or conclusions should be made regarding the safety or effectiveness of the unapproved use of an approved product.

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.

1.1C 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)
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)
sNDA/sBLA submission date	List the date of sNDA/sBLA submission to the FDA
FDA Advisory Committee meeting	List the date of the planned or anticipated FDA Advisory Committee meeting

Continues.

Type of Information	*Description of Information*
PDUFA or FDA approval date	List the date or time frame (e.g., 2023, Q1'22) of anticipated FDA approval
Approval dates and indications in other countries (outside of the United States)	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 completed, 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 completed, key endpoints, and number of patients; provide links to Clinicaltrials.gov or PubMed
Anticipated routes and dosing information	Describe the route(s) of administration 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 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 United States	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 United States	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 product

FDA = U.S. Food and Drug Administration; HCDM = health care decision-maker; PDUFA = Prescription Drug User Fee Act; sBLA = supplemental biologics license application; sNDA = supplemental new drug application.

2.0C PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1C PRODUCT DESCRIPTION

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[1]; AMCP Format recommendation[2]):

1. A clear statement that the unapproved use of an approved product is not FDA approved, and that the safety or effectiveness of the unapproved use has not been established.[1]
2. Information related to the phase of product development (e.g., the status of any studies in which a new use is being investigated and how it relates to the overall product development plan, whether a marketing application for the new use has been submitted to the FDA or when such a submission is planned).[1]
3. Product information.[1]
    - Attach the full FDA-approved prescribing information.[2]
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 subjects enrolled, subject enrollment criteria, subject demographics).[1]
5. Anticipated timeline for possible commercialization (e.g., FDA approval/clearance/licensure of the unapproved use of an approved product).[1]
    - Date of supplemental NDA, supplemental BLA.[2]
    - Date of FDA advisory committee review, if any.[2]
    - Date of anticipated FDA approval/clearance/licensure.[2]

6. Product pricing information.[1]
    - See Section 4.0C.[2]
    - Information may be provided here or in Section 4.0C.[2]
7. Patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).[1]
8. Product-related programs or services (e.g., patient support programs).[1]
9. 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).[1]
    - See Section 3.0C.[2]
    - Information may be provided here or in Section 3.0C.[2]
10. Other factual information per the manufacturer's discretion.[2]

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 specifics of an unapproved use are 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 unapproved use. That said, HCDMs need to know basic disease-related information when reviewing information about unapproved uses.

Manufacturers are requested to provide as much information as possible about the medical condition or disease state for which the unapproved use is being studied and FDA approval is being sought without making characterizations or conclusions about the safety or effectiveness of the unapproved use. This is true especially with rare or orphan diseases. The intent is to give the reader an overall sense of the disease. The disease description should be brief and should include epidemiology, risk factors, pathology, 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 new 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 the 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 all clinical studies that support the unapproved use of an approved product, reported in a clear and concise format.

Manufacturers should provide factual presentations of results from studies, including clinical studies of the unapproved use or bench tests that describe product performance for the unapproved use. No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved use. Manufacturers should describe material aspects of study design and methodology and disclose material limitations related to the study design, methodology, and results. Manufacturers should also ensure that information and results are not selectively presented (e.g., both positive and negative or null findings should be presented).

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.

Typical information may include, but is not limited to phase 1, 2, and 3 studies (e.g., peer-reviewed publications; medical congress abstracts, posters, presentations); information from Clinicaltrials.gov; pre-clinical studies; data on file per manufacturers' discretion.

Manufacturers may use discretion to provide information in the form of study summaries only or evidence tables only or both.

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, 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., number intended 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.

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 <one page (maximum two) for each study.

Evidence tables should include the following items where available and applicable:

1. Citation (if unpublished, "data on file"), Clinicaltrials.gov ID number.
2. Treatments, sample size, length of follow-up.
3. Study design, inclusion and exclusion criteria.
4. Primary and secondary endpoints, results (when available).

4.0C ECONOMIC INFORMATION

The price of the product is already known for the approved product and should be included in the Unapproved Use Dossier. Describe any potential or anticipated changes in the costs based on the unapproved use of the approved product.

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.

APPENDIX A
ADDITIONAL TERMS AND DEFINITIONS

Biosimilars: A biosimilar is 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."[42]

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.[66]

Care Pathways: Care pathways have been used widely in health care, and while definitions vary, care pathways are generally characterized as a method for 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.[70]

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 to make informed decisions that will improve health care at both the individual and population level.[71]

Companion Diagnostic Test (CDT): Companion diagnostic tests have been defined in various ways. The U.S. Food and Drug Administration definition describes a CDT as one that provides information that is essential for the safe and effective use of a corresponding therapeutic product.[34] 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 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.[72]

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 his or her own view.[72]

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).[72]

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.[72]

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 measured of utility or preference, often as a quality-adjusted life-years gained. Cost-utility analysis can be considered the "gold standard" methodology for evaluating the cost-effectiveness of health care choices.[72]

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 determine systematically the relative value of alternative courses of action.[72]

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.[72]

Effectiveness: The *actual* effects of treatment by the drug under "real life" conditions (e.g., patients not always remembering to take their doses, physicians often not prescribing the lowest U.S. Food and Drug Administration recommended doses, side effects not all controlled). Head-to-head effectiveness studies with similar medications are preferable.

Efficacy: The *potential* effects of treatment by the drug under optimal circumstances (e.g., patients all taking their doses at the right times, physicians prescribing U.S. Food and Drug Administration [FDA] recommended doses, side effects appropriately monitored). Efficacy studies are typically the foundation of new drug submissions to the FDA. Studies that compare the efficacy of similar drugs, rather than just efficacy compared 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-makers' expertise and the appraisal of the clinical evidence base are current and up to date.[73]

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, related products, and 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, 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 analyses 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.[72]

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 as a whole form the individual's perspective. (See Patient-Reported Outcomes.)[72]

Incremental Cost-effectiveness Ratio (ICER): The ICER is a common metric used to evaluate results of cost-effectiveness and cost-utility analyses. The ICER is the difference in costs divided by the difference in outcomes between two comparators.[72]

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.[72]

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.[74]

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.[72]

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.[72]

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.[72]

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.[72]

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]

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 and:

- No alternate 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 must apply to only a very small number of patients.[75]

Sensitivity Analysis: A way to analyze the effect of uncertainty in an economic analysis or a decision (see Decision Analysis, 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 evaluated.[72]

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, Risk Evaluation and Mitigation Strategy programs, data collection, or administration) or patient management before or following administration (monitoring, disease, or therapeutic support systems).[76]

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.[72]

APPENDIX B
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-based 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 all the [Organization Name] Pharmacy and Therapeutics Committees to make evidence-based decisions representing good value for money 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 C
FORMULARY MONOGRAPH TEMPLATE

INDIVIDUAL DRUG REVIEW

Generic Name: [Name]

Brand Name: [Name]

Company: [Text]

Date of Review: [Month/Year]

Reason for Review: [Text]

TABLE OF CONTENTS:

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:

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

[Narrative summary of evidence for efficacy.]

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

[Narrative summary of evidence for comparative effectiveness.]

Issue 3: What is the evidence of safety?

[Narrative summary of evidence for safety.]

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

Summary of Product Value

[Text summary statement.]

Incremental Cost-effectiveness

[Discussion of cost-effectiveness analyses.]

Summary of Incremental Cost-effectiveness Ratios Found by Studies Included in this Review

[Text or table to summarize study findings.]

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

[Discussion of patient subgroups and the evidence that would indicate improved incremental cost-effectiveness ratio for these subpopulations. Include a description of relevant biomarkers or other companion diagnostics that would be used to identify these target populations, and the feasibility of using these markers in routine clinical practice.]

TABLES

Clinical Evidence Summary

Ref. and Evidence Grade	*Drug Regimens*	*n*	*Time*	*Demographics*	*Design**	*Endpoints/ Results/ Comments*	*Number Needed to Treat*

AC = active control; CCS = case-control study; DB = double-blind; PC = placebo control; PCS = prospective cohort study; PG = parallel group; MA = meta-analysis; MC = multicenter; RCS = retrospective cohort study; RCT = randomized controlled trial; XO = crossover.

Validation of Instruments Used in Studies

Name of Instrument	*Abbreviation*	*Description*	*Numerical Scale*	*Interpretation of Values*	*MID**

MID = minimal important difference.

**MID is usually determined by the originator or owner of the instrument. This number represents a threshold below which a numerical difference is not considered to be clinically meaningful, even if statistically significant. Differences less than this amount are usually excluded from discussions of incremental clinical effect.*

Cost-effectiveness Evidence Summary

(Table format may be modified it needed to better fit the economic study methodology.)

Ref. and Sponsor	*QHES Score*	*Study Design and Treatments Compared*	*Time Horizon and Demographics*	*Model Inputs and Data Sources*	*Results: Base Case, Sensitivity Analysis, and Limitations*

LYS = life-years saved, QALY = quality-adjusted life-year; QHES = Quality of Health Economic Studies; QOL = quality of life.

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.]

PHARMACOKINETICS

[Text summary, if kinetics will factor significantly into the decision.]

Route of Administration

Bioavailability

Time to Peak

Multiple Dosing

Clearance

ADVERSE EVENT PROFILE

[Brief text summary of known side effects and general tolerability from the package insert or other available sources. If clinically important, include a brief table of side effects from the package insert, 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 package insert. 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

1. Neumann PJ, Cohen JT. Measuring the value of prescription drugs. *N Engl J Med.* 2015;373(27):2595-97. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/26580666.*** Accessed October 19, 2019.

2. Bach PB. New math on drug cost-effectiveness. *N Engl J Med.* 2015;373(19):1797-99. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/26535510***. Accessed October 19, 2019.

3. U.S. Food & Drug Administration. Drug and device manufacturer communications with payors, formulary committees, and similar entities — questions and answers: guidance for industry and review staff. June 2018. Available at: h***ttps://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537347.pdf.*** Accessed October 19, 2019.

4. Food and Drug Administration Modernization Act of 1997, 21 USC §114 (1997). Available at: ***https://www.govinfo.gov/app/details/PLAW-105publ115.*** Accessed October 19, 2019.

5. Coalition Working Group (AMCP, Alliance of Community Health Plans, American Medical Association, American Society of Health-System Pharmacists, Department of Veterans Affairs, National Business Coalition on Health, U.S. Pharmacopeia). Principles of a sound drug formulary system. October 2000. Available at: ***https://www.amcp.org/sites/default/files/2019-03/Principles%20of%20a%20Sound%20Drug%20Formulary%20System.pdf.*** Accessed October 19, 2019.

6. Tyler LS, Cole SW, May JR, et al; ASHP Expert Panel on Formulary Management. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. *Am J Health Syst Pharm.* 2008;65(13):1272-83. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/18589893.***

7. Schiff GD, Galanter WL, Duhig J, et al. A prescription for improving drug formulary decision making. *PLoS Med.* 2012;9(5):1-7. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22629233.*** Accessed October 19, 2019.

8. U.S. Food and Drug Administration. 21 CFR Part 202 - Prescription Drug Advertising (1962). Available at: ***https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=202.*** Accessed October 19, 2019.

9. 21st Century Cures Act. Public Law No.114-255 (2016). Available at: ***https://www.govinfo.gov/content/pkg/PLAW-114publ255/html/PLAW-114publ255.htm.***

10. U.S. Food & Drug Administration. Responding to unsolicited requests for off-label information about prescription drugs and medical devices. Draft guidance. December 2011. Available at: ***http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf.*** Accessed October 19, 2019.

11. AMCP. The AMCP format for formulary submissions (version 4.0). April 2016. Available at: ***http://www.amcp.org/FormatV4/.*** Accessed October 19, 2019.

12. Berry DA. Bayesian approaches for comparative effectiveness research. *Clin Trials.* 2012;9(1):37-47. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/21878446.*** Accessed October 19, 2019.

13. U.S. Food & Drug Administration. Guidance for the use of Bayesian statistics in medical device clinical trials. February 5, 2010. Available at: ***http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf.*** Accessed October 19, 2019.

14. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol.* 2009;62(5):464-75. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/19348971.*** Accessed October 19, 2019.

15. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA.* 2003;290(12):1624-32. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/14506122.*** Accessed October 19, 2019.

16. Berger ML, Dreyer N, Anderson F, Towse A, Sedrakyan A, Normand SL. Prospective observational studies to assess comparative effectiveness: the ISPOR good research practices task force report. *Value Health.* 2012;15(2):217-30. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22433752.*** Accessed October 19, 2019.

17. Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part III. *Value Health.* 2009;12(8):1062-73. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/19793071.*** Accessed October 19, 2019.

18. Institute of Medicine. *Finding What Works in Health Care: Standards for Systematic Reviews.* Washington, DC: The National Academies Press; 2011. Available at: ***https://iom.nationalacademies.org/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-Systematic-Reviews/Standards.aspx.*** Accessed October 19, 2019.

19. Agency for Healthcare Research and Quality (AHRQ). Methods guide for effectiveness and comparative effectiveness reviews. AHRQ Publication No. 10(14)-EHC063-EF. January 2014. Available at: ***https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-methods-guide_overview.pdf.*** Accessed October 19, 2019.

20. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the Drug Effectiveness Review Project. *BMC Med Res Methodol.* 2012;12(1):140.

21. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health.* 2011;14(4):429-37. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/21669367.*** Accessed October 19, 2019.

22. Jaime Caro J, Briggs AH, Siebert U, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices—overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—1. *Value Health.* 2012;15(6):796-803. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999128.*** Accessed October 19, 2019.

23. CER Collaborative. Comparative Effectiveness Research Tool. Available at: ***https://www.cercollaborative.org/global/default.aspx?RedirectURL=%2fhome%2fdefault.aspx.*** Accessed October 19, 2019.

24. Berger ML, Martin BC, Husereau D, et al. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):143-56. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/24636373.*** Accessed October 19, 2019.

25. Jaime Caro J, Eddy DM, Kan H, et al; ISPOR-AMCP-NPC Modeling CER Task Forces. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):174-82. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/24636375.*** Accessed October 19, 2019.

26. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):157-73. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/24636374.*** Accessed October 19, 2019.

27. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care.* 2010;48(6 Suppl):S145-52. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/20473206.*** Accessed October 19, 2019.

28. Ollendorf DA, Pearson SD. ICER evidence rating matrix: a user's guide. February 2016. Updated July 18, 2017. Available at: ***https://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf.*** Accessed October 19, 2019.

29. CER Collaborative. Synthesizing a Body of Evidence Tool. Available at: ***https://www.cercollaborative.org/modules/module.aspx?ModuleID=10&CTRL=Page&ContentID=2&ContentTypeID=10.*** Accessed October 19, 2019.

30. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-26. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/18436948.*** Accessed October 19, 2019.

31. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol.* 2011;64(4):380-82. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/21185693.*** Accessed October 19, 2019.

32. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force procedure manual. December 2015. Available at: ***https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual.*** Accessed October 19, 2019.

33. U.S. Food & Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. August 31, 2017. Available at: ***https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.*** Accessed October 19, 2019.

34. U.S. Food & Drug Administration. In vitro companion diagnostic devices - guidance for industry and Food and Drug Administration staff. August 6, 2014. Available at: ***http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf.*** Accessed October 19, 2019.

35. Canestaro WJ, Pritchard DE, Garrison LP, Dubois R, Veenstra DL. Improving the efficiency and quality of the value assessment process for companion diagnostic tests: the Companion test Assessment Tool (CAT). *J Manag Care Spec Pharm.* 2015;21(8):700-12. Available at: ***https://www.jmcp.org/doi/10.18553/jmcp.2015.21.8.700.*** Accessed October 19, 2019.

36. U.S. Food & Drug Administration. Framework for regulatory oversight of laboratory developed tests (LDTs). Draft guidance. October 3, 2014. Available at: ***http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf.*** Accessed October 19, 2019.

37. U.S. Food & Drug Administration. FDA notification and medical device reporting for laboratory developed tests (LDTs). Draft guidance. October 3, 2014. Available at: ***http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416684.pdf.*** Accessed October 19, 2019.

38. Hinman LM, Huang SM, Hackett J, et al. The drug diagnostic co-development concept paper: commentary from the 3rd FDA-DIA-PWG-PhRMA-BIO Pharmacogenomics Workshop. *Pharmacogenomics J.* 2006;6(6):375-80. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/16652120.*** Accessed October 19, 2019.

39. Centers for Disease Control and Prevention. ACCE model process for evaluating genetic tests. December 28, 2010. Available at: ***http://www.cdc.gov/genomics/gtesting/ACCE/index.htm.*** Accessed October 19, 2019.

40. Institute of Medicine. *Generating Evidence for Genomic Diagnostic Test Development: Workshop Summary.* Washington, D.C.: The National Academies Press; 2011. Available at: ***http://www.nap.edu/catalog.php?record_id=13133#toc.*** Accessed October 19, 2019.

41. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. *Med Decis Making.* 1991;11(2):88-94. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/1907710.*** Accessed October 19, 2019.

42. U.S. Food & Drug Administration. Questions and answers on biosimilar development and the BPCI Act - guidance for industry. December 2018. Available at: ***https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-biosimilar-development-and-bpci-act-guidance-industry.*** Accessed October 19, 2019.

43. U.S. Food & Drug Administration. Considerations in demonstrating interchangeability with a reference product: guidance for industry. May 2019. Available at: ***https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry.*** Accessed October 19, 2019.

44. Biologics Price Competition and Innovation (BPCI) Act of 2009. Public Law No. 111-148 (2009). Available at: ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf.*** Accessed October 19, 2019.

45. U.S. Food & Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product — guidance for industry. April 2015. Available at: ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*** Accessed October 19, 2019.

46. U.S. Food & Drug Administration. Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry — guidance for industry. April 2019. Available at: ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf.*** Accessed October 19, 2019.

47. U.S. Food & Drug Administration. Nonproprietary naming of biological products: update — guidance for industry. March 2019. Available at: ***https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf.*** Accessed October 19, 2019.

48. U.S. Food & Drug Administration. Reference product exclusivity for biological products filed under Section 351(a) of the PHS Act. Draft guidance. August 2014. Available at: ***https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf.*** Accessed October 19, 2019.

49. U.S. Food & Drug Administration. Clinical pharmacology data to support a demonstration of biosimilarity to a reference product: guidance for industry. December 2016. Available at: ***https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf.*** Accessed October 19, 2019.

50. U.S. Food & Drug Administration. New and revised draft Q&As on biosimilar development and the BPCI Act (revision 2): guidance for industry. December 2018. Available at: ***https://www.fda.gov/regulatory-information/search-fda-guidance-documents/new-and-revised-draft-qas-biosimilar-development-and-bpci-act-revision-2.*** Accessed October 19, 2019.

51. Varadhan R, Segal JB, Boyd CM, Wu AW, Weiss CO. A framework for the analysis of heterogeneity of treatment effect in patient-centered outcomes research. *J Clin Epidemiol.* 2013;66(8):818-25. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/23651763.*** Accessed October 19, 2019.

52. Malone DC, Hines LE, Graff JS. The good, the bad, and the different: a primer on aspects of heterogeneity of treatment effects. *J Manag Care Pharm.* 2014;20(6):555-63. Available at: ***https://www.jmcp.org/doi/10.18553/jmcp.2014.20.6.555.*** Accessed October 19, 2019.

53. Warholak TL, Hilgaertner JW, Dean JL, et al. Evaluation of an educational program on deciphering heterogeneity for medical coverage decisions. *J Manag Care Pharm.* 2014;20(6):566-73. Available at: ***https://www.jmcp.org/doi/10.18553/jmcp.2014.20.6.566.*** Accessed October 19, 2019.

54. Willke RJ, Zheng Z, Subedi P, Althin R, Mullins CD. From concepts, theory, and evidence of heterogeneity of treatment effects to methodological approaches: a primer. *BMC Med Res Methodol.* 2012;12:185. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/23234603.*** Accessed October 19, 2019.

55. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials.* 2010;11:85. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/20704705.*** Accessed October 19, 2019.

56. Adapted with permission from: Carlson J, Veenstra DL, Ramsey SD, Garrison LP, Sullivan SD, Carlson R; the University of Washington. Guidance for the submission of evidence supporting coverage and reimbursement decisions for medical tests (version May 12, 2010; unpublished source on file).

57. U.S. Food & Drug Administration. Adaptive designs for clinical trials of drugs and biologics - guidance for industry. September 2018. Available at: ***https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf.***

58. U.S. Food & Drug Administration. Adaptive designs for medical device clinical studies: guidance for industry and Food and Drug Administration staff. July 27, 2016. Available at: ***https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-designs-medical-device-clinical-studies.*** Accessed October 19, 2019.

59. Physician Payments Sunshine Act, Section 6002 of the Affordable Care Act. Public Law No. 111-148 (2010). Available at: ***https://www.govinfo.gov/content/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf.*** Accessed October 19, 2019.

60. Briggs AH, Weinstein MC, Fenwick EA, et al; ISPOR-SMDM Modeling Good Research Practices Task Force. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—6. *Value Health.* 2012;15(6):835-42. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999133.*** Accessed October 19, 2019.

61. Eddy DM, Hollingworth W, Caro JJ, et al; ISPOR–SMDM Modeling Good Research Practices Task Force. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—7. *Value Health.* 2012;15(6):843-50. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999134.*** Accessed October 19, 2019.

62. Karnon J, Stahl J, Brennan A, et a; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—4. *Value Health.* 2012;15(6):821-27. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999131.*** Accessed October 19, 2019.

63. Pitman R, Fisman D, Zaric GS, et al; ISPOR-SMDM Modeling Good Research Practices Task Force. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—5. *Value Health.* 2012;15(6):828-34. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999132.*** Accessed October 19, 2019.

64. Roberts M, Russell LB, Paltiel AD, et al; ISPOR-SMDM Modeling Good Research Practices Task Force. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—2. *Value Health.* 2012;15(6):804-11. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999129.*** Accessed October 19, 2019.

65. Siebert U, Alagoz O, Bayoumi AM, et al; ISPOR-SMDM Modeling Good Research Practices Task Force. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—3. *Value Health.* 2012;15(6):812-20. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/22999130.*** Accessed October 19, 2019.

66. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health.* 2014;17(1):5-14. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/24438712.*** Accessed October 19, 2019.

67. Mauskopf JA, Sullivan SD, Annemans L, et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices—budget impact analysis. *Value Health.* 2007;10(5):336-47. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/17888098.*** Accessed October 19, 2019.

68. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in Health and Medicine.* New York, NY: Oxford University Press; 1996.

69. Husereau D, Drummond M, Petrou S, et al; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value Health.* 2013;16(2):e1-5. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/23538200.*** Accessed October 19, 2019.

70. Chawla A, Westrich K, Matter S, Kaltenboeck A, Dubois R. Care pathways in US healthcare settings: current successes and limitations, and future challenges. *Am J Manag Care.* 2016;22(1):53-62. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/26799125.*** Accessed October 19, 2019.

71. Institute of Medicine. *Initial National Priorities for Comparative Effectiveness Research.* Washington, DC: The National Academies Press; 2009. Available at: ***http://www.nationalacademies.org/hmd/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx.*** Accessed October 19, 2019.

72. Berger ML, Bingefors K, Hedblom EC, Pashos CL, Torrence GW, eds. *Health Care Cost, Quality, and Outcomes: ISPOR Book of Terms.* Lawrenceville, NJ: ISPOR; 2003.

73. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ.* 1996;312(7023):71-72. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/8555924.*** Accessed October 19, 2019.

74. Weinstein MC, O'Brien B, Hornberger J, et al; ISPOR Task Force on Good Research Practices—Modeling Studies. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling Studies. *Value Health.* 2003;6(1):9-17. Available at: ***https://www.ncbi.nlm.nih.gov/pubmed/12535234.*** Accessed October 19, 2019.

75. Richardson J, McKie J. The rule of rescue. Centre for Health Program Evaluation. Working paper 112. Available at: ***https://www.sciencedirect.com/science/article/abs/pii/S0277953602002447?via%3Dihub.*** Accessed November 19, 2019.

76. AMCP. The AMCP format for formulary submissions (version 3.1). Addendum: specialty pharmaceuticals. December 2012. Available at: ***https://www.amcp.org/sites/default/files/2019-03/Format%20Version%203.1%20Final%202.2013_0.pdf.*** Accessed October 19, 2019.

675 N Washington Street | Suite 220
Alexandria, VA 22314

703.684.2600 | www.amcp.org | @amcp.org