PREFACE

The need to carefully evaluate and balance considerations related to treatment benefit, cost-effectiveness, and affordability has never been greater. This is validated by the recent proliferation of initiatives by a number of health care organizations to develop value frameworks with the objective of providing a more rigorous and comprehensive assessment of value when considering the adoption of new health technologies, including new pharmaceutical products.[1,2]

Since its initial release in 2000, the AMCP *Format for Formulary Submissions* has provided a framework to advise drug manufacturers regarding important payer evidence requirements as it relates to evaluating new technologies for formulary consideration. With the release of the *Format*, Version 4.0, we have attempted to incorporate updated considerations related to fostering rigorous, relevant, and ongoing scientific dialogue between manufacturers and health care decision makers (HCDM's) as it relates to assessing the safety, efficacy, and value of new health technologies. Additionally, we have addressed evolving considerations in the health care environment, including considerations related to biosimilars, medical devices, comparative effectiveness research, and specialty pharmaceuticals, to name a few. Guidance on logistical matters related to updating dossiers, the challenge of providing pre-approval dossiers, and ongoing communication between manufacturers and HCDM's is provided as well.

Structurally, we have provided guidance on some of these key contextual considerations in the introductory section of the *Format*, while specific guidance related to content requirements for each section of the dossier are provided in those sections, as in previous versions of the *Format*.

[1] Neumann PJ, Cohen JT. Measuring the value of prescription drugs. *N Eng J Med*. 2015;(epub ahead of print):1-4. Available at http://www.nejm.org/doi/full/10.1056/NEJMp1512009. Accessed 12/7/15.
[2] Bach PB. New math on drug cost-effectiveness. *N Eng J Med.* 2015;373(19):1707-17999. Available at http://www.nejm.org/doi/full/10.1056/NEJMp1512750. Accessed 12/7/15.

THE ROLE OF THE AMCP FORMAT

The evidence requirements outlined in the AMCP *Format* are intended for use by manufacturers who are responding to an unsolicited request from HCDMs to support coverage, reimbursement, and/or formulary placement of new and existing drugs, tests, or devices or class of drugs, tests, or devices.

The *Format* supports the informed selection of drugs, tests, and devices by:

- Identifying the clinical and economic evidence required for the evaluation of drugs, tests, and devices
- Standardizing the synthesis and organization of the evidence in a concise document also known as the "AMCP dossier" or "product dossier
- Providing the manufacturer the ideal opportunity to communicate the value of a product that is grounded in evidence-based medicine principles
- Supporting the unsolicited request process that manufacturers must abide by in order to provide comprehensive information that goes beyond a product's FDA-approved label
- Requiring economic models and projections of product impact on the organization and its enrolled population
- Encouraging a clear, transparent, and two-way communication process between manufacturers and HCDMs

The AMCP *Format* is designed to maintain a high standard of objectivity and credibility to achieve two important goals.

First, it is intended to improve the timeliness, scope, quality, and relevance of clinical and economic information provided by manufacturers to HCDMs. Further, by assessing the healthcare system impact of using a product, the evidence requested can improve the HCDM's ability to compare the effects of formulary alternatives on clinical outcomes, value, and economic consequences for the entire healthcare system.

Second, the AMCP *Format* streamlines the evidence acquisition and review process for HCDMs and healthcare system staff. By clearly specifying the standards of evidence implicit in the existing formulary process, the *Format* furnishes pharmaceutical manufacturers with consistent direction concerning the nature and format of information that is expected. In addition, the standardized format allows healthcare system staff to formally evaluate the completeness of submissions received and to easily add the results of the healthcare system's own systematic literature reviews and analysis. Manufacturers should understand that submission of information in the recommended format does not guarantee approval of their product for formulary listing. Manufacturers and HCDMs should view discussion about, and subsequent submission of a dossier, as a process to improve the quality and layout of information provided, but not as a formula for approval. The *Format* offers a clear, shared vision of the requirements to facilitate the collaboration necessary between HCDMs and manufacturers to support appropriate and evidence-based product evaluation. Recognizing that manufacturers may not have all the requested evidence, especially for new products, the *Format* describes the information requirements necessary to support a comprehensive assessment of the proposed product.

The Academy of Managed Care Pharmacy views the AMCP *Format* as a template or guide that has become the gold standard in requesting and receiving clinical and economic evidence from manufacturers for the purpose of evaluating the value of drugs, tests, and devices. While it is up to individual healthcare systems to decide how they operate their formulary review processes, AMCP urges HCDMs to request product dossiers in the AMCP *Format* from manufacturers when evaluating drugs, tests, and devices for coverage, reimbursement, and formulary decisions. The aim of the *Format* is to provide evidence requirements that meet the evidence needs of all HCDMs and healthcare systems. Though the AMCP *Format* Executive Committee recognizes that there are other formats, guidelines, and value frameworks

issued by other organizations, it also regards the adoption and use of *Format* as a best practice for the formulary review process.

The AMCP *Format* does not specify methods for assessing clinical benefit, harms, or economic impact, however the evidence presented should meet accepted standards of evidence-based medicine and health technology assessment. It is the manufacturer's responsibility to utilize appropriate study designs, analytic techniques, and data sources. Likewise, it is the requester's responsibility to critically evaluate the evidence supplied.

GENERAL TOPICS RELATED TO FORMAT V.4.0

The following are general topics related to Format v.4.0. Some of these provide additional guidance related to terminology used in the Format. Other sections include guidance related to logistical considerations related to developing and maintaining dossiers, while other sections focus on content areas of relevance to the Format that were raised by internal and external stakeholders.

DECISION MAKERS AND MANUFACTURERS

The term "healthcare decision maker' (HCDM) and healthcare system is used throughout this document to refer to ANY healthcare personnel, committee, or organization that uses an evidence-based process for making healthcare coverage and reimbursement decisions 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 (HTA) organizations, and other organized healthcare systems.

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

COMMUNICATIONS BETWEEN HCDMS AND MANUFACTURERS

Communications between HCDMs and pharmaceutical or device manufacturers are strictly regulated by the FDA. The FDA considers proactive, solicited communications to be "promotional" and requires the content of the communications to be limited to information in the FDA approved product label. The Food, Drug, and Cosmetic Act was amended in 1997 (FDAMA Section 114) to allow proactive, solicited communications about "health care economic information" to a limited audience of "formulary committees and similar entities".[3] The use of FDAMA Section 114 by manufacturers to date has been limited but recent first amendment challenges to FDA regulations on "promotion" and attempts by Congress to update the FDAMA Section 114 language could potentially allow more proactive, solicited communications in the future. In the meantime, since FDAMA Section 114 was intended to inform HCDMs of health care economic information, HCDMs should clearly articulate to manufacturers what information is needed and how it should be delivered.[4]

In addition to proactive, solicited communications, the FDA also allows manufacturers to reactively respond to unsolicited requests for information from HCDMs. It is this unsolicited request process that has historically been used for communications involving the AMCP Format – this unsolicited process continues to be the mechanism through which the AMCP Format Version 4.0 can and should be communicated to HCDMs.

AMCP dossiers developed according to the *Format* should be treated under the unsolicited request process by manufacturers because the Format calls for information that goes beyond the product label Therefore, at no time, shall an evidence dossier in the AMCP *Format* be sent to a HCDM or healthcare

[3] FDA. Food and Drug Administration Modernization Act (FDAMA) of 1997. Public Law 105-115, November 21, 1997. Available at: http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm. Accessed 12/8/15.
[4] Perfetto EM, Burke L, Oehrlein EM, et al. FDAMA Section 114: why the renewed interest? *J Manag Care Spec Pharm*. 2015;21(5):368-374. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=19494.

system without an authentic, validated unsolicited request from the requestor directly to the manufacturer. Any violation of this rule, intentional or not, jeopardizes the regulatory safe harbor for unsolicited requests that allows industry to prepare and respond to requests for product dossiers in the AMCP *Format*, as well as the Academy's original intent and mission for the *Format*.

In December 2011, the FDA issued a draft guidance called "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 how manufacturers drugs and medical devices can respond to unsolicited requests for information about products.[5]

To qualify as 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 dossier that it is being provided in response to an unsolicited request.

Substantial on-going communication between the healthcare system and manufacturers throughout the product evaluation process is critical to manage expectations and maximize the quality of available evidence. When a dossier is requested from a healthcare system, it is important for that organization to communicate to the manufacturer basic information such as review timelines, the evaluation process, and any special needs that might exist. This allows the manufacturer an opportunity to provide timely, relevant, and specific information that meets the needs of the healthcare system. If manufacturers cannot provide specific information, it is better to understand the limitations 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.

Healthcare systems need and want to know about new product and new indication launches for their planning purposes. Therefore, manufacturers should keep healthcare systems informed about the status of their pipeline, especially anticipated new product or new indication launches in the near future, e.g., 3 to 6 months prior to FDA approval.

Dossiers have often been criticized by HCDMs about being 'biased'. Therefore, HCDMs should express any concerns or questions about the evidence presented in a dossier, including assumptions related to economic models, to facilitate a productive dialogue with manufacturers. Feedback from dossier users can help improve the quality of dossiers developed and provided by manufacturers.

CONFIDENTIALITY

The confidentiality of evidence dossiers has been an area of concern since AMCP published the first version of the *Format* in October 2000. Manufacturers have expressed concern that confidential information submitted as part of an evidence dossier, e.g., unpublished studies, off-label information, economic modeling data, will become publicly available, thus exposing sensitive data to competitors, and potentially alarming regulatory authorities worried about misleading promotion. To a large extent, the concerns should be addressed through compliance with FDA guidance on unsolicited requests and with appropriate confidentiality agreements between the healthcare system and the manufacturer. Healthcare systems 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 US, the UK, and certain other countries are made available to

[5] FDA. Draft guidance: responding to unsolicited requests for off-label information about prescription drugs and medical devices. December 2011. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf. Accessed 11/15/15.

the public but commercial-in-confidence information, when properly identified by the manufacturer, is redacted for the online version of the report. Special arrangements with public payers, which require public disclosure of information received, may be necessary.

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

Product dossiers prepared in accordance with the evidence requirements contained in the AMCP *Format* may contain off-label information and information deemed proprietary by the product manufacturer. Therefore, such dossiers may only be distributed in response to an unsolicited request.

Manufacturers should place a statement on the dossier that a confidentiality agreement was executed, if one was put in place.

COMPARATIVE EFFECTIVENESS RESEARCH (CER)

While the AMCP *Format* does not require manufacturers to use any particular research design to present evidence of benefit, harms, 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 FDA approval 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 should 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 can be used to conduct CER. The *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,[6,7] pragmatic clinical trials,[8,9] prospective observational studies,[10] retrospective observational

[6] Berry DA. Bayesian approaches for comparative effectiveness research. *Clin Trials*. 2012;9(1):37-47. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4314707/pdf/nihms657573.pdf.
[7] FDA. Guidance for the use of Bayesian statistics in medical device clinical trials. February 2010. Available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf. Accessed 12/9/11.
[8] 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):464-475. Available at: http://www.cmaj.ca/content/180/10/E47.full.pdf+html.
[9] 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):1624-1632. http://www.ncbi.nlm.nih.gov/pubmed/?term=tunes+stryer+practical+clinical+trials+2003
[10] Berger ML, Dreyer N, Anderson Fred, et al. Prospective observational studies to assess comparative effectiveness: the ISPOR Good Research Practices Task Force Report. *Value Health.* 2012;15:217-230. Available at: http://www.ispor.org/taskforces/documents/pos_assesscompeffectivenessgrptfreport.pdf.

studies,[11] systematic evidence reviews[12,13,14] including indirect treatment comparisons and network meta-analyses,[15] and modeling studies.[16]

The CER Collaborative (www.cercollaborative.org), formed by AMCP, ISPOR (International Society for Pharmacoeconomics and Outcomes Research) and NPC (National Pharmaceutical Council), developed the CER Tool[17] to assist HCDMs in the evaluation and use of four types of outcomes research: prospective and retrospective observational studies,[18] modeling studies,[19] and indirect treatment comparison studies.[20]

DOSSIER FOR DRUGS, TESTS, AND DEVICES

While the original AMCP *Format* was developed to address evidence for drugs (pharmaceuticals, biologics, and vaccines), today, *the Format* aims to also provide guidance for developing dossiers for non-drug products (e.g., tests and devices) that may be relevant to healthcare systems' drug formulary and medical policy decisions.

Specifically, Version 4.0 has been updated to include guidelines on the evidentiary requirements for companion diagnostic tests (CDT) that was first introduced in Version 3.1 as an addendum to the *Format* (see Section 2.3).

Additionally, the *Format* can be used to convey evidentiary requirements for medical devices. Due to 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 be relevant and applicable for the *Format*. Examples of medical devices where the *Format* may apply include, but 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 manufacturers are encouraged to develop and make available medical device dossiers for HCDMs and health systems upon unsolicited requests.

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[11] Johnson ML, Crown W, Martin BC, et al. 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 in Health*. 2009;12(8):1062-1073. Available at: https://www.ispor.org/TaskForces/documents/RDPartIII.pdf.

[12] Institute of Medicine (IOM). *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 11/26/15.

[13] Agency for Healthcare Research and Quality (AHRQ). Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: January 2014. Available at www.effectivehealthcare.ahrq.gov. Accessed 11/26/15.

[14] Oregon Health and Science University (OHSU). Drug Effectiveness Review Project. Systematic review methods and procedures. 2011. Available at http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. Accessed 11/26/15.

[15] 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;14:429-437. Available at: http://www.ispor.org/workpaper/conducting-Indirect-treatment-comparison-and-network-meta-analysis-studies.pdf.

[16] Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices - overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Value Health*. 2012;15:796-803. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf.

[17] CER Collaborative. Comparative Effectiveness Research Tool. Available at https://www.cercollaborative.org/global/default.aspx?RedirectURL=%2fhome%2fdefault.aspx. Accessed 11/26/15.

[18] Berger ML, Martin BC, Husereau D, et al. 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: 143-156. Available at: https://www.ispor.org/observational-health-study-use-guideline.pdf.

[19] Caro JJ, Eddy DM, Kan H, et al., A modeling study questionnaire to assess study relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17:174–182. Available at: https://www.ispor.org/modeling-health-study-use-guideline.pdf

[20] 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;17:157-173. Available at: https://www.ispor.org/indirect-treatment-study-use-guideline.pdf.

As such, language in the *Format* has been revised to refer to a "product" throughout which may be a drug, a test, or a device. Where a specified requirement does not apply, the manufacturer may indicate "not applicable". AMCP recognizes the challenge of adapting the *Format* to medical devices without providing explicit requirements and encourages manufacturers to use sound judgment in providing objective information and relevant evidence about a product that will meet the needs of HCDMs and healthcare systems.

COMPANION DIAGNOSTIC TESTS (CDT)

Companion diagnostic tests (CDTs) have been defined in various ways, and has 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 (IVD companion diagnostic device) as one that provides information that is essential for the safe and effective use of a corresponding therapeutic product.[21]

More specifically, in the *Format*, a CDT is defined as a laboratory test or assay that provides predictive and differential information about patients' response to drug therapy. This is in contrast to diagnostic or prognostic tests, which provide information about the disease process rather than response to treatment. Canestaro et al. (2015) has 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. The full publication provides a user-friendly, step-by-step algorithm and key questions to help HCDMs make these assessments. [22]

The reader is referred to other sources for background information regarding CDTs.[23,24,25] In addition, a number of other CDT evidence gathering and evaluating frameworks have been developed.[26,27,28,29,30]

Dossier from Drug Manufacturer vs CDT Manufacturer

Implementation of dossier requests for CDTs using the *Format* may be complicated by the variety of potential relationships between a drug manufacturer and CDT manufacturer/developer. The following are possible CDT development scenarios (in no order of preference):

- CDT co-developed with drug, and FDA-approved together with drug
- CDT developed independently of drug, typically after drug approval

[21] FDA. Guidance: in vitro companion diagnostic devices. August 2014. Available at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf Accessed 11/15/15.
[22] Canestaro WJ, Pritchard DE, Garrison LP, et al. 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(3):700-712. Available at: http://www.npcnow.org/system/files/research/download/companion-diagnostics.pdf.
[23] FDA. Draft guidance: framework for regulatory oversight of laboratory developed tests (LDTs). October 2014. Available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf. Accessed 11/28/15.
[24] FDA. Draft guidance: FDA notification and medical device reporting for laboratory developed tests (LDTs). October 2014. Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416684.pdf. Accessed 11/28/15.
[25] FDA. Drug-diagnostic co-development concept paper. April 2005. Available at http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf. Accessed 7/30/12.
[26] Centers for Disease Control and Prevention, Office of Public Health Genomics. "ACCE" model process for evaluating genetic tests. Available at http://www.cdc.gov/genomics/gtesting/ACCE/index.htm. Accessed 7/30/12.
[27] IOM. Generating evidence for genomic diagnostic test development: workshop summary. 2011. Available at: http://www.nap.edu/catalog.php?record_id=13133#toc. Accessed 7/30/12.
[28] AHRQ. U.S. Preventive Services Task Force procedure manual. AHRQ Publication No. 08-05118-EF, July 2008. Available at http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. Accessed 11/28/15.
[29] AHRQ. Methods guide for medical test reviews. AHRQ Publication No. 12-EC017, June 2012.. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews_Full-Guide_20120530.pdf. Accessed 7/30/12.
[30] *Fryback D. Thornbury J. The efficacy of diagnostic imaging. Med Decis Making. 1991;11: 88 -94.* http://www.ncbi.nlm.nih.gov/pubmed/1907710

- CDT developed independently and targeted for class of medications

In each of these scenarios, the drug manufacturer may or may not be the same as the CDT manufacturer. In the case where the drug manufacturer is different from the CDT manufacturer, the two companies may or may not have business agreements to work collaboratively in the development and/or 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 lab-developed test (LDT) developed by clinical laboratories and not FDA approved. Thus, depending on the development pathway, drug manufacturers and CDT developers may have different responsibilities and processes with regard to evidence submission to health care decision makers.

Given the potential complexity of regulatory processes, data sources, and manufacturer relationships, the *Format* recommends the following approaches for developing dossiers with CDT evidence:

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

BIOSIMILARS

As FDA-approved biosimilars reach the market, formulary decision makers may require a body of efficacy, safety, economic, and comparative effectiveness data similar to that of the innovator product in order to make rational, evidence-based decisions regarding coverage and reimbursement. In response to unsolicited requests, manufacturers of biosimilars should develop and provide product dossiers like those of the innovator products.

The extent and scope of animal and human studies needed for biosimilar product development programs may differ markedly from those of generic versions of non-biologic products. In addition, FDA has stated that the type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity and/or interchangeability will be determined on a product-specific basis. Biosimilars do not fit the definition of a generic equivalent product, i.e., identical or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Biosimilars are not generic biologics. As such, manufacturers of biosimilars should incorporate these considerations into the dossier to allow HCDMs to fully evaluate these products.

For more information, FDA has released several guidance documents:

- 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[31]

[31] FDA. Information for industry (biosimilars). Last updated 8/27/2015. Available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241720.htm. Accessed on 11/15/15.

- Biologics Price Competition and Innovation Act of 2009 (BPCI Act).[32]
- Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. April 2015[33]
- Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. April 2015[34]
- Guidance for Industry: Nonproprietary Naming of Biological Products. Draft Guidance, August 2015[35]
- Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act. Draft Guidance, August 2015[36]
- Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Draft Guidance, May 2014[37]
- Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. April 2015[38]
- Draft Guidance for Industry: Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. May 2015.[39]

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."[40] 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 individual patient variability, variability within populations studied, and variability between clinical studies. Malone et al. has developed tools for HCDMs to assess whether clinically relevant differences exist between individuals, populations, or clinical trials.[41]

[32] Biologics Price Competition and Innovation (BPCI) Act of 2009. Public Law No. 111-148. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf. Accessed on 11/15/15.
[33] FDA. Guidance: scientific considerations in demonstrating biosimilarity to a reference product. April 2015. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed on 11/15/15.
[34] FDA. Guidance: quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product. April 2015. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf. Accessed on 11/15/15.
[35] FDA. Draft guidance: nonproprietary naming of biological products. August 2015. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf. Accessed 11/15/15.
[36] FDA. Draft guidance: reference product exclusivity for biological products filed under Section 351(a) of the PHS Act. August 2014. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf. Accessed on 11/15/15.
[37] FDA. Draft guidance: clinical pharmacology data to support a demonstration of biosimilarity to a reference product. May 2014. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf. Accessed on 11/15/15.
[38] FDA. Guidance: biosimilars - questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. April 2015. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf. Accessed on 11/15/15.
[39] FDA. Draft guidance: biosimilars - additional questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. May 2015. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf. Accessed on 11/28/15.
[40] Varadhan R, Segal JB, Boyd CM, et al. A framework for the analysis of heterogeneity of treatment effect in patient-centered outcomes research. *J Clin Epidemiol. 2013;*66(8):818-825. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450361/pdf/nihms693584.pdf.
[41] 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):555-563. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=18151.

UPDATING DOSSIERS

A common question from manufacturers is, "When should a dossier be updated?" Dossiers should 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 impacts the overall evidence. While most healthcare systems request dossiers for products when they are newly approved by the FDA, dossiers should be used beyond initial launches for subsequent product or class reviews. Ideally, dossier updates should be evidence-based, i.e., updates are triggered by availability of new evidence, for example:

1. 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
2. The FDA issues advisory statements about the use of a product, e.g. established a new boxed warning, etc.
3. Significant new clinical or economic evidence becomes available that may (not exhaustive list):
    a. Further support the use of the product for the approved indication
    b. Identify patients or sub-populations who should or should not receive the product
    c. Demonstrate real world effectiveness and long-term effectiveness
    d. Elucidate long-term safety

When updating a dossier, the manufacturer may conduct a complete revision to incorporate new evidence, delete obsolete information, and revise content and format, resulting in a new version of the dossier, or amend existing dossier with a supplemental document that acknowledges new evidence with proper citations, identifies obsolete information in the existing dossier, and describes any addition modifications relevant to the HCDM. The manufacturer should provide HCDMs with a way to identify newly added information, e.g., highlighting revised/new sections or content, describe changes in an appendix, include a summary of changes in a cover letter, etc.

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, evaluate for technical accuracy on an annual basis, e.g., price increase, new model assumptions, etc. All dossiers should have the original date of issue as well as the dates of any revisions or reviews for potential revisions.

When a HCDM requests a dossier that is under revision, the manufacturer should supply the current version of the dossier, inform the requestor of the status of the dossier and the expected timeframe 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 had previously requested and received a dossier?" In general, manufacturers should not freely and automatically send updated dossiers to previous requestors without an unsolicited request; in other words, another unsolicited request from the HCDM is required in order to send an updated dossier. However, as a result of AMCP's previous discussions with FDA regulatory staff, a HCDM may, at the time of original 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 months. The request for updated dossiers should not be indefinite. Adherence to 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 dossier within a specific time frame will help manufacturers maintain compliance to the unsolicited request process.

The manufacturer may determine that a dossier will no longer be kept current, e.g., the product is near the end of its branded lifespan. If the manufacturer continues to provide the dossier to requesters, then this status should be indicated on the dossier. If the manufacturer discontinues the availability of the dossier, then a rationale for its discontinuation should be provided to requesters of that dossier.

Development and organization of the dossier for a product with multiple FDA approved indications should be handled at the discretion of the manufacturer. For example, manufacturer may develop separate sections for each indication within the same dossier, or may develop separate dossiers for each indication or group of indications.

PRE-APPROVAL DOSSIERS

It is not uncommon for healthcare systems to want a dossier well before FDA approval. In fact, this is one of the most common comment received from HCDMs about dossiers.

For regulatory and compliance reasons, manufacturers are limited in what they can proactively communicate before FDA approval. Furthermore, it is not possible for manufacturers to provide a full dossier that meets all the requirements of the *Format* prior to product approval by the FDA. For example, it is not possible for manufacturers to provide the cost or price of the product before final FDA approval.

However, manufacturers are able to provide certain information, generally public or published data, regarding product before FDA approval upon an unsolicited request to the company's medical information or medical communications department. The information provided depends on 1) the HCDM's specific unsolicited request, and 2) the information that the manufacturer deems appropriate and available to provide.

Thus, manufacturers may use the current *Format* as a template to provide information where feasible in response to a HCDM's request for a "dossier" before a product's FDA approval. In general, this information is in the public domain in some fashion, and may rarely include data on file. This "pre-approval" or "pre-launch dossier" may include, but is not limited to:

1. Clinical trial information from Phase 1, Phase 2, and Phase 3 studies
    - Peer-reviewed publications
    - Medical congress abstracts, posters, presentations
    - Medical information or medical communication departments' response letters
2. Information from clinicaltrials.gov
3. Pre-clinical studies
4. Data on file per manufacturer's discretion
5. Disease state information, e.g., disease description, epidemiology, clinical presentation, currently available therapies, clinical practice guidelines, etc.
6. Pipeline product information, e.g., proposed mechanism of action
7. Any other information that a manufacturer deems relevant to the request and allowable according to the manufacturer's policies and procedures
8. Some manufacturers may consider providing certain information under a confidentiality agreement

MEDIA FOR DOSSIER AND MODEL SUBMISSIONS

Manufacturers should submit dossiers in an electronic format rather than in print. This will help reduce resource expenditures and improve healthcare system staff's ability to transfer evidence directly into P&T committee submission monographs. **In addition manufacturers must provide a transparent,**

unlocked copy of the model without a graphical interface. It should be presented electronically as an Excel workbook, ASCII tab-delimited file or an alternative electronic format that is agreed upon by the requesting organization or its consultants and the manufacturer.

IMPLEMENTATION OF VERSION 4.0

A new dossier under development or an existing dossier being updated at the time of Version 4.0 release may be converted to the new *Format* with relative ease. If creation or revision of the dossier is close to completion at the time of Version 4.0 release (e.g., approximately than half complete), then adherence to Version 3.1 is an option.

For a subsequent revision of an existing dossier that commences after the release of Version 4.0, conversion to Version 4.0 is highly recommended.

Development of a new dossier that commences *after* the release of Version 4.0 (after April 2016) should comply with Version 4.0 of the *Format*.

EVIDENCE REQUIREMENTS FOR FORMULARY SUBMISSION

1.0 EXECUTIVE SUMMARY – CLINICAL AND ECONOMIC VALUE OF THE PRODUCT

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 from Sections 2 through 5, and it should be representative of the body of evidence found in Sections 2 through 5. The manufacturer should briefly describe the clinical and economic information presented in the dossier using the layout prescribed in Sections 1.1 and 1.2 and state the expected per unit product cost. Based on this information, the manufacturer should articulate a value argument to justify these expected expenditures for this product in the context of its anticipated effects on the clinical evidence, health outcomes, and the economic consequences for the healthcare 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.

1.1 CLINICAL BENEFITS

Begin with the FDA-approved indication 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:

- Efficacy and Effectiveness
- Comparative effectiveness relative to available alternative therapies
- Safety/tolerability
- Shortcomings of current treatment and the unmet medical need that the PROPOSED THERAPY addresses

1.2 ECONOMIC BENEFITS

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

- Cost per unit
- Context of the proposed cost: potential clinical benefits provided (including quality of life benefits) and potential economic benefits (including savings or cost offsets)
- 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 (ICER) result at minimum. Briefly summarize other published information on the cost or economic impact of the product (such as impact of resource utilization or other cost offsets).

Include the economic impact of special handling, delivery, route and site of administration, REMS programs, and other administrative offsets that would be above and beyond the cost of the product.

1.3 CONCLUSIONS

Summarize the value of the proposed product. Highlight key points regarding the clinical and economic advantages and uniqueness of the product are highlighted. Finally, based on the information presented in Sections 2 to 5 that follow, the conclusions should include a statement

regarding the expected impact of the product, relative to other available treatment options both pharmaceutical and non-pharmaceutical.

2.0 Product Information and Disease Description

2.1 Product Description

Manufacturers are required to provide detailed information about their product. They should compare the new product with other products commonly used to treat the condition, whether or not these products are currently on the healthcare system's formulary.

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 also contains 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, etc.). Verbatim language from the PI do not need to be supplied here. If there is not 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/or dosing) is of major significance in defining the value of a product, additional information beyond 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 (NDC) 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 (HCPCS) codes applicable to these products, as well as any Current Procedural Terminology (CPT) codes that are relevant to reimbursement. International Classification of Diseases (ICD)-10 codes are also advisable to include for any indications specified in the PI.
4. The ASP and WAC cost per unit size (the payers contract price, if available, should be included as well)
5. AHFS or other Drug Classification
6. FDA approved indication(s) and the date approval was granted (or is expected to be granted). Also other significant off-label uses and potential new indications being studied.
7. Pharmacology*
8. Pharmacokinetics/Pharmacodynamics*
9. Contraindications*Warnings/Precautions/Adverse Effects*
10. Interactions* with suggestions on how to avoid them
    - Drug/Drug
    - Drug/Food
    - Drug/Disease
11. 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

12. Access, e.g. restrictions on distribution, supply limitations, anticipated shortages, and/or prescribing restrictions
    - For a specialty pharmaceutical, this section should be expanded up 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; access assistance information
13. Co-Prescribed / Concomitant Therapies, including dosages, recommended use of other agents or treatments with the product, and the rationale and clinical benefit associated with the co-prescribed/concomitant therapies.
14. 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 product(s) or services that the proposed product is expected to substitute for, or replace. This information should be presented in tabular form. 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 of the dossier. Include outcomes whether in product label or not, i.e., include relevant on- and off-label information.
15. For biosimilar products, comparator information about the innovator product should be included as well as evidence that demonstrate biosimilarity or interchangeability
16. Describe how product may impact quality measures, e.g., HEDIS scores. Include studies that support this information in Section 3 or 5.

*Verbatim language from the Approved Package Insert should not be supplied here. If there is not substantive data or information that can be provided beyond the label, these sections should be left blank and the reader referred to the copy of the PI which is in the Appendix.

2.2 Place of the Product in Therapy

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

2.2.1 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. Ideally, information should be provided in a table or bulleted list.

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

a) Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product
b) Pathophysiology
c) Clinical presentation
d) Societal, humanistic and/or economic burden

Specialty pharmaceuticals often treat rare diseases that may be unfamiliar, with relatively little information available in the public domain. This section may be expanded to provide greater detail for rare conditions treated with specialty pharmacy.

2.2.2 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 VERY brief summary of information from the literature for each topic; do not duplicate information included in other sections:

a. Summarize current approaches to treatment including principal therapeutic options (drug and non-drug), common practice patterns, or standards of care; include recommendations supported by well-accepted or nationally recognized clinical practice guidelines and consensus statements.
b. 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, including comparative effectiveness of product relative to alternative therapies
c. Indicate the appropriate care setting(s) for the product such as self-administration by the patient, by a health care professional in the home, in an infusion therapy clinic, in a physician office, or in a hospital.
d. 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 and supported with evidence.
e. Include proposed ancillary disease or care management intervention strategies to be 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 3.0 or 5.0 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.
f. Disclose other product development or post-marketing obligations as required by the FDA such as a Risk Evaluation and Mitigation Strategy (REMS), Phase IV 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 multi-faceted program intended to accompany the product at launch will include REMS alongside other elements, describe it in section 2.2.2.e and note in 2.2.2.f that the program contains a REMS component.
g. Describe the expected outcome(s) of therapy, e.g. a cure, palliation, relief of symptoms, quality of life, patient reported outcomes, productivity, etc. Describe any clinical markers that that are linked to disease outcome, e.g. LDL lowering.
h. Other key assumptions and their rationale.

2.2.3 Relevant Treatment Guidelines and Consensus Statements from National and/or International Bodies

This section should describe the treatment guideline's position on the therapy. Include position statements and validated tools from national organizations and international HTA bodies, e.g., NICE. Next, an attempt should be made to generalize these findings to the populations of the requesting organization. Discuss the implications of any differences that exist between the literature and typical practice patterns and patient populations. When more than one disease is addressed, complete the description for each separate condition. The requesting organization and the manufacturer should determine the relevant treatment options for comparison during the initial pre-submission meeting.

2.3 Evidence for Companion Diagnostic Tests

2.3.1 Product Information

When a CDT has been co-developed with a drug, or when the CDT is required per FDA labeling, then the three elements, clinical validity, clinical utility, and economic value, will generally be captured in the drug dossier according to the *Format*. However, in cases where the CDT is not inherently tied to the drug evidence, then the CDT developer should respond to an unsolicited request with a separate CDT dossier.

a. Generic name, brand name, manufacturer or clinical laboratory
b. Type of test: technical, e.g., immunohistochemical (IHC), fluorescent in situ hybridization (FISH), gene expression profile, etc.
c. Target: describe test target, e.g., biomarker, microarray patter, etc.
d. FDA cleared or approved indication(s)/use(s) with companion drug
e. Date of FDA clearance or approval
f. Intended use: clinical basis for CDT, e.g., diagnosis, prognosis and management, risk management, treatment, monitoring or pre-symptomatic testing
g. Indication and target population(s); prevalence of disease/condition and CDT variant in target population
h. Place of CDT in drug therapy
i. Contraindications, warnings/precautions, interactions relative to CDT use
j. Alternative tests and options available, whether they are CDTs or LDTs; describe relative advantages and disadvantages
k. Other key assumptions and their rationale
l. Supporting clinical and economic evidence for the test, using ACCE framework:
    1. 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
    2. Clinical Validity: How well does the test identify the disease or medical condition of interest?
        - Positive predictive value (PPV): how often does a patient that tests positive have the medical condition?

- Negative predictive value (NPV): how often does a patient that tests negative not have the medical condition?
- Threshold(s) used to separate a positive from a negative result
- In which populations has the test been validated, and in how many studies?

3. Clinical Utility: How does the test improve patient outcomes?
   - Interventions that are based on positive and negative test resutls
   - Efficacy/effectiveness and safety of the clinical intervention implemented as a result of the test
   - Changes in patient outcomes, treatments received, clinical events, impact on disease progressions, risk-benefit assessment, morbidity, quality of life, survival, etc.
   - Consider inclusion of quantitative risk-benefit decision analytic modeling
4. Economic Value
   - What is the expected difference in costs and outcomes with test compared to usual care, including cost offsets from changes in drug utilization, side effect treatment, and other healthcare 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 gained, etc.

m. Packaging description, regulatory codes, classification(s), and identifiers
n. Billing and reimbursement codes, price
o. Copy of the product label or package insert

2.3.2 PLACE OF CDT IN CLINICAL PRACTICE

CDT manufacturers or providers who develop a stand-alone CDT dossier should include the following information:

a. Disease description
   a. Epidemiology and relevant risk factors
   b. Pathophysiology
   c. Clinical presentation
   d. Societal and/or economic impact of disease
b. Approaches to treatment
   a. Diagnosis (principal options, practice patterns, alternative options)
   b. Anticipated use of test in patient management
   c. Prognosis (expected intermediate health outcomes, expected net health outcomes of treatment, etc.)
   d. Relevant clinical practice guidelines, clinical pathways, health technology assessments, systematic reviews
   e. Other key assumptions and their rationale

2.3.3 SUPPORTING CLINICAL DATA

Where there are studies pertaining to the CDT that do not belong in Section 3.0, summarize those studies in this section.

For CDT manufacturers or providers who develop a stand-alone CDT dossier, all clinical trials that include the CDT should be summarized in this section.

Submit summaries of key studies that have been conducted, whether published or not, for example:

- Analytical validation studies
- Clinical validation studies
- Clinical utility studies (randomized trials, prospective effectiveness trials, case series, retrospective studies, systematic reviews, meta-analyses)
- 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 (PRO) studies, quality of life studies)
- Safety studies

Evidence in summaries should include:

a. Setting and location of study
b. Study design, Research question(s)
c. Inclusion and exclusion criteria
d. Patient characteristics (demographics, number studied, disease severity, comorbidities)
e. Intervention and control group
f. Patient follow-up procedures (e.g., if an intention-to-treat design is used, were drop-outs followed and for what time period?); Treatment/follow up period
g. Clinical outcome(s) measures
h. Outcomes evaluated
i. Delineate primary vs. secondary study endpoints and their corresponding results
j. Other results/outcomes reported (e.g., quality of life, assay performance)
k. Principal findings
l. Statistical significance of outcomes and power calculations
m. Validation of outcomes instrument (if applicable)
n. Compliance behavior
o. Generalizability of the population treated
p. Relevance to enrolled populations
q. Publication citation(s)/references used
r. State whether trials or other studies for the product are registered in a public trials registry, and if so, provide access information (e.g. www.clinicaltrials.gov)

3.0 PRIMARY CLINICAL EVIDENCE

Section 3.0 should consist of all primary clinical studies that support the use and value of the product reported in a clear and concise format. Specifically, primary clinical studies that investigate any aspect of the product directly in patients, i.e., research conducted in patients, regardless of study design should be included. This includes interventional studies, studies that require obtaining patient consent, or 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, long-term safety, patient preference, patient adherence, patient reported outcomes, quality of life, evidence that identify patient subgroups or clinical setting that may be more appropriate, and other clinically-related outcomes.

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 comparative effectiveness research be incorporated into the product dossier. The payer is 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, primary clinical evidence that are relevant for this section include the following criteria:

1. FDA-approved indications and unapproved uses
    - Potential off-label uses are of significant interest to HCDMs. As such, clinical studies involving off-label uses must be included in dossiers. Manufacturers should clearly delineate evidence for on- and off-label uses, e.g., organize and report on-label indication(s) and information first and off-label thereafter.
2. Published and unpublished studies and data
    - Studies available from published journals; medical congress abstracts, posters, and presentations; manuscripts submitted or accepted by medical journals, clinicaltrials.gov, press releases, manufacturers' data on file
3. Any study design
    - While specific study designs are not prescribed in this section, manufacturers should include studies that generate evidence from studying patients directly which may include, for example, randomized controlled trials (Phase 2, 3, 4), open-label studies, pragmatic trials, observational or cohort studies, registries, case series, case reports, and surveys
    - Studies may have one or more study arms
4. Study results regardless of positive, negative, or null findings
5. U.S. and ex-U.S. studies
6. Relevant data and findings from the FDA and other governmental agencies
7. Ongoing clinical trials and links to their registry information
8. *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 easy. 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 manufacturer 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's suggested that in such cases, the evidence be separated into three different 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 consort diagram. Considerations for establishing inclusion or exclusion criteria may be, but 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), etc.

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 evidence table row, 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 5.0

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 should decide 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 data that is available. It must be noted that HCDMs want concise, focused, and user-friendly presentation of data. The *Format* no longer dictates the number of pages or length for study summaries, however it is strongly recommended that manufacturers use good judgment in managing the length of dossiers. One of the most common complaint from HCDMs is that dossiers are too long.

The manufacturer should grade all studies listed in the dossier, based on a recognized method to evaluate quality of studies and should identify which method is being used. Where possible, provide a link to original sources if they are free.

The manufacturer should provide journal reprints, copies of congress abstracts, posters, and presentations, and other available study information upon request by HCDMs.

For drugs designated by the FDA as "breakthrough drugs" the evidentiary requirements are the same as for other drugs. For drugs determined to be "biosimilars," basic evidentiary requirements 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.

3.1 Study Summaries

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

1. Publication citation(s), 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 (ITT, per protocol, etc.)
7. Treatments and interventions, dosage regimens, washout period, concomitant therapies, etc.
8. Clinical outcome(s) evaluated, measured, and collected, delineating primary vs secondary endpoints as well as pre-specified vs post hoc
9. 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

3.2 Evidence Tables

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/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/or statistical significance. Within the Results column, include a table of key results.
9. Statistical significance

In general, an evidence table for an individual study should fit on one page. It may be helpful to display evidence tables in landscape rather that portrait formats with appropriate use of abbreviations and other acceptable ways to display data in a clear, objective, and concise way.

4.0 Economic Value and Modeling Report

4.1 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 healthcare system the risk-benefit tradeoff of the product, and its economic value.

4.1.1 Utility 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 and 5 of the AMCP *Format*, and are the core of evidence-based decision-making. These data, however, may have important limitations for decision-making. For example,

- Randomized controlled trials (RCTs) may not include all relevant comparator interventions

- The duration of follow-up in RCTs may be limited
- Patient populations in RCTs may not be reflective of plan populations
- Safety data may be limited, or from disparate sources
- Healthcare cost impacts may not be generalizable across payers

These limitations have led to recent efforts in comparative effectiveness research to improve the quantity, diversity, and relevance of information available to healthcare decision makers. Comparative effectiveness data – derived from studies including relevant populations, comparators, and outcomes - will prove valuable to healthcare system formulary decision makers, and should be reported in Section 3 of the *Format*. 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 healthcare technologies. They are disease-based and take into account the impact 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 impacts, and the costs of the interventions. Decision models can provide:

- An explicit framework for decision-making;
- A synthesis of evidence on health consequences and costs from many different sources;
- A formal assessment of uncertainty;
- A quantitative measure of clinical risk-benefit;
- Explicit and evaluable assumptions;
- Specificity for a product's role or place in therapy; and
- 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.

4.1.2 TYPES OF MODELS

Cost-effectiveness models.

These models address the question "Is the technology good value for the money?" There are several types of models that can be helpful for managed care decision makers. The focus of the AMCP Format is the clinical and economic value of products for plans and their members. Evaluations that include impacts on patients – e.g., morbidity and mortality – and on healthcare 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 healthcare 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 utilize clinical data and can be relatively

complex, and thus should follow the recommendations in this section, as well as published best practices.[42,43,44,45,46,47,48]

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 in a payer-relevant timeframe. Budget impact models are not intended to establish the overall value of healthcare technologies because they do not include the full impact of the technology on clinical and patient outcomes. They can be useful for estimating system-wide (e.g., pharmacy and medical) budget impacts, however, and are commonly used by managed care payers. These models, as defined here, estimate the target population, drug/product costs, healthcare cost offsets, and adverse event costs, as well as the expected utilization in the healthcare system, to derive projected per member per month costs. Budget impact models utilize clinical data and can be relatively complex, and thus should follow the recommendations in this section, and published best practices.[49,50]

Financial models.

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

4.1.3 OTHER CONSIDERATIONS

- A clear, written statement of the decision problem, modeling objective, and scope of the model should be developed. This should include: the spectrum of disease

[42] Briggs AH, Weinstein MC, Fenwick EAL, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health*. 2012;15(6):835-842. Available at: https://www.ispor.org/workpaper/Modeling_Methods/Model_Parameter_Estimation_and_Uncertainty-6.pdf.
[43] Caro JJ, Briggs AH, Siebert U, et al. 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: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf.
[44] Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health*. 2012;15(6):843-850. Available at: http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf.
[45] Karnon J, Stahl J, Brennan A, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value Health*. 2012;15(6):821-827. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_using_Discrete_Event_Simulation-4.pdf.
[46] Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--5. *Value Health*. 2012;15(6):828-834. Available at: https://www.ispor.org/workpaper/Modeling_Methods/Dynamic_Transmission_Modeling-5.pdf.
[47] Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value Health*. 2012;15(6):804-811. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Conceptualizing_a_Model-2.pdf.
[48] Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health*. 2012;15(6):812-820. Available at: http://www.ispor.org/workpaper/Modeling_Methods/State-Transition_Modeling-3.pdf.
[49] 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: http://www.ispor.org/budget-impact-health-study-guideline.pdf.
[50] 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):336-347. Available at: http://www.ispor.org/workpaper/research_practices/Principles_of_Good_Research_Practices-Budges_Impact_analysis.pdf.

925 considered, perspective of the analysis, target population, alternative interventions,
926 health and other outcomes, and time horizon.
927 • The International Society for Pharmacoeconomics and Outcome Research (ISPOR)
928 and Society for Medical Decision Making (SMDM) have produced comprehensive
929 guidance related to various aspects of modeling. [51,52,53,54,55,56,57] ISPOR-SMDM best
930 practices should be followed when applicable.
931 • When a product is intended for treatment of more than one disease or indication, its
932 impact should be modeled for each, unless a reasonable case can be made for a single
933 model, such as may be the case for budget impact models.
934 • Models that have been previously developed may be adapted for use according to the
935 AMCP Format. An existing model should be modified to follow the general
936 framework described in this document and must be able to demonstrate the system-
937 wide impact of introducing the product to healthcare system formularies. Evidence
938 supporting the validity of existing models should be provided, as well as sufficient
939 documentation on their design, functioning, and data inputs.
940 • Cost-effectiveness analyses conducted alongside RCTs, particularly when of
941 sufficient size and follow-up can provide useful and sometimes substantial evidence
942 of economic value. Cost-effectiveness models should be considered complementary
943 to such studies, allowing for the adjustment of healthcare resource use, unit costs,
944 effectiveness, and practice patterns.
945 • All assumptions should be clearly presented.
946 • Specialty pharmaceuticals should generally be addressed similarly to traditional
947 pharmaceutical products. Additional considerations may be required for site of care
948 (e.g. inpatient, home infusion, outpatient infusion center).
949 • Due to similarity to their reference product, biosimilars generally do not require the
950 development of specific cost-effectiveness models. Budget impact models or cost-
951 minimization analyses may be more relevant.
952 • When possible a standalone, electronic, unlocked, modifiable model should be
953 provided to payers. The use of commonly available software (e.g. Microsoft Excel) is
954 recommended. The model should be interactive and flexible, allowing the user to
955 choose which inputs to include in the model and the ability to tailor inputs to their
956 health system or health plan.

[51] Briggs AH, Weinstein MC, Fenwick EAL, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health*. 2012;15(6):835-842. Available at: https://www.ispor.org/workpaper/Modeling_Methods/Model_Parameter_Estimation_and_Uncertainty-6.pdf.
[52] Caro JJ, Briggs AH, Siebert U, et al. 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: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf.
[53] Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health*. 2012;15(6):843-850. Available at: http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf.
[54] Karnon J, Stahl J, Brennan A, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value Health*. 2012;15(6):821-827. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_using_Discrete_Event_Simulation-4.pdf.
[55] Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--5. *Value Health*. 2012;15(6):828-834. Available at: https://www.ispor.org/workpaper/Modeling_Methods/Dynamic_Transmission_Modeling-5.pdf.
[56] Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value Health*. 2012;15(6):804-811. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Conceptualizing_a_Model-2.pdf.
[57] Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health*. 2012;15(6):812-820. Available at: http://www.ispor.org/workpaper/Modeling_Methods/State-Transition_Modeling-3.pdf.

- Lastly, users of this document should recognize the Format is a set of recommendations on the types of evidence and reporting formats that are likely to be useful for managed care decision makers. We recognize the need for flexibility, however. Specific requirements are determined by individual managed care organizations, and may consist of data requests or methods beyond those outlined in this document.

4.2 Modeling Approaches and Methods

Manufacturers should consult with healthcare system staff in the early stages of model development to identify optimal modeling approaches and ensure the incorporation of appropriate comparator products and endpoints to reflect clinical reality.

4.2.1 Cost –Effectiveness Analysis Approach and Framework

Guidelines

In general, the cost-effectiveness framework should consider recommendations published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society of Medical Decision Making (SMDM) Modeling Good Research Practices Task Force. [58,59,60,61,62,63,64]

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

a) Disease or condition, patient population, natural history, clinical course and outcomes.
b) Relevant treatment options and the treatment process for each option – preferably based on treatment guidelines or Actual practice
c) Costs of product and other medical resources consumed within each clinical pathway.
d) Outcomes of therapy for each clinical pathway
e) 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/or quality-adjusted life-years

[58] Briggs AH, Weinstein MC, Fenwick EAL, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health*. 2012;15(6):835-842. Available at: https://www.ispor.org/workpaper/Modeling_Methods/Model_Parameter_Estimation_and_Uncertainty-6.pdf.
[59] Caro JJ, Briggs AH, Siebert U, et al. 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: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf.
[60] Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health*. 2012;15(6):843-850. Available at: http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf.
[61] Karnon J, Stahl J, Brennan A, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value Health*. 2012;15(6):821-827. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Modeling_using_Discrete_Event_Simulation-4.pdf.
[62] Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--5. *Value Health*. 2012;15(6):828-834. Available at: https://www.ispor.org/workpaper/Modeling_Methods/Dynamic_Transmission_Modeling-5.pdf.
[63] Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value Health*. 2012;15(6):804-811. Available at: http://www.ispor.org/workpaper/Modeling_Methods/Conceptualizing_a_Model-2.pdf.
[64] Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health*. 2012;15(6):812-820. Available at: http://www.ispor.org/workpaper/Modeling_Methods/State-Transition_Modeling-3.pdf.

(QALYs). Clinical events are more readily interpretable by clinicians and allow for direct assessment of the impact of clinical data, but cost per event avoided calculations are not comparable across disease areas. In contrast, QALYs allow for assessment of overall healthcare value, but may be more difficult to interpret from a healthcare 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 timeframe 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, primarily related to the conflicting factors of transparency and data availability vs. the complexity of many diseases and their treatments. It is recommended that the simplest feasible modeling approach be utilized. 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 Timeframe

The payer perspective is recommended for the primary analysis, with optional perspectives (i.e., 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. Multiple timeframes are recommended for chronic disease – e.g., 5-year, 10-year, and lifetime. Adjustment for time preference should be incorporated as appropriate and follow US PHS Panel recommendations (discounting both future costs and health effects).[65]

4.2.2 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 of the data in the model should be clear and systematic.

It is important that modeled claims for cost-effectiveness derive from data from one or more comparative effectiveness trials. These should:

- Directly or indirectly compare and quantify treatment effects and other relevant patient-reported outcomes (including quality of life)
- Assess patient and community preferences for alternative therapies;
- Quantify costs and benefits over the natural course of the disease;

[65] Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York, NY, Oxford University Press, 1996.

- Assess resources used to support alternative therapies; and
- Evaluate the impact 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 *Format*. 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, randomized, controlled trial 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, this 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. 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 healthcare system data. If specific healthcare 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 EQ-5D, HUI, SF-6D, or QWB.

Demographic and practice pattern data

Ideally the model would will be interactive, allowing demographic and practice pattern data from the healthcare system to be incorporated 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 normal 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 vs. 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 in order for healthcare system staff to evaluate the validity of this approach.

4.2.3 ANALYSIS

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 healthcare cost offsets vs. drug costs should be displayed independently and combined. Clinical risk-benefit tradeoffs should be explicitly presented and discussed.

Sensitivity analysis

Both univariate and probabilistic sensitivity analyses should be conducted to provide a more complete picture regarding the robustness of the results. Comprehensive one-way sensitivity analysis of all parameters in the model is strongly recommended, including assessment of impacts 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 when data are stochastic. The use of tornado diagrams is encouraged to identify the most sensitive parameters. The 3-5 parameters and 2-3 assumptions that have the greatest impact 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..

4.3 BUDGET IMPACT MODEL APPROACH AND FRAMEWORK

Guidelines

The modeling approach and analytic framework of the budget impact model should generally follow the guidance provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[66,67]

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

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

Perspective and Timeframe

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

[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: http://www.ispor.org/budget-impact-health-study-guideline.pdf.

[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):336-347. Available at: http://www.ispor.org/workpaper/research_practices/Principles_of_Good_Research_Practices-Budges_Impact_analysis.pdf.

Population

The target population for a budget impact model should include all patients eligible for the new intervention during the time frame of interest.

4.3.1 DATA SOURCES

The model should be provided to the end user in an unlocked modifiable electronic format to allow the end user to input local health system specific data. The model should be interactive and flexible, allowing the user to choose which inputs to include in the model and the ability to tailor inputs to their health system.

4.3.2 ANALYSIS

Results

When reporting the economic impact of the intervention, it is recommended to present the findings as both the cost per member per month (PMPM) and as the total budget impact to 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.

4.4 MODELING REPORT AND INTERACTIVE MODEL

4.4.1 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 the negative effects of 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.[68] Therefore, researchers are encouraged to focus efforts on the clarity and transparency of results. Detailed descriptions that explain the flow of data through the model are recommended. All calculations should be explained in a simple straightforward manner to allow a non-health economist to comprehend the analysis. This information and references should be accessible both in the report format as well as shown directly in the model to optimize ease of review.

Listed below are the recommended requirements for modeling reports and interactive models.

4.4.2 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

[68] Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health*. 2012;15(6):843-850. Available at: http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf.

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, etc.) may be used if needed.

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 upon which sensitivity analyses are based for each input.

a) Include references in the table for all inputs, including ranges.
b) Note in the table 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 healthcare system formulary committees. The following specific data should be presented for each strategy as appropriate for the analysis type:

a) The projected clinical events (e.g., heart attacks, cirrhosis, recurrence)
b) The life expectancy and QALY estimates
c) Total healthcare costs
d) The cost of implementing therapy, including all anticipated costs of care management, delivery, administration, and setting of care, and the resulting cost offsets
e) 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.

a) Clearly present the model inputs or assumptions that drive the difference in 1) costs, 2) effects, and 3) incremental cost-effectiveness.
b) When appropriate, present multi-way (e.g., 2-way, best/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 Format revision is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement.[69] This statement provides additional guidance regarding preferred

[69] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*. 2013;16(2):231-250. Available at: http://www.ispor.org/ValueInHealth/ShowValueInHealth.aspx?issue=3D35FDBC-D569-431D-8C27-378B8F99EC67.

reporting standards for economic evaluations. For reference, the CHEERS Checklist is provided in Appendix "X".

4.4.3 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 for use if clearly documented in peer-reviewed publications and a users manual. Interactive models should have the following characteristics:

- All data and calculations relevant to the cost-effectiveness model should be contained in the spreadsheet and visible to the user.
- All inputs should be modifiable by the user.
- 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.
- Allow for analysis of relevant sub-populations (age, gender, co-morbidities) where applicable.
- Allow the healthcare system to incorporate its own data (membership size, prevalence rates, cost estimates, etc.) in place of default data, such as national norms.
- Provide automated 1-way sensitivity analysis.

Model accessibility

It is recommended that the healthcare 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 payer'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, although such arrangements are significantly less desirable. Manufacturers are also encouraged to publish economic models in the peer-review 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.

5.0 Secondary Clinical Evidence and Non-Clinical Studies

Section 5.0 should consist of all other types of evidence and studies that do not fit in Section 3.0 that support the use and value of the product reported in a clear and concise format. Examples of evidence in this section includes clinical practice guidelines (CPGs), health technology assessments (HTAs) and systematic reviews (SRs), compendia, meta-analyses, and non-clinical studies such as administrative claims analyses, modeling and pharmacoeconomic studies.

Similar to Section 3.0, evidence reported in this section include the following relevancy criteria: FDA-approved indications and unapproved uses; published and unpublished studies and data; any study regardless of study design; study results regardless of positive, negative, or null findings; and U.S. and ex-U.S. studies.

5.1 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 consensus statements and clinical pathways 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 be included in or influenced by the guidelines. Summarize information from clinical practice guidelines briefly and provide a copy of the full guidelines upon request.

5.2 Health Technology Assessments and Systematic Reviews

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

5.3 Compendia

Summarize important information found in compendia that are officially recognized by the Secretary of Health and Human Services that list the product. If these references are available only by subscription, provide PDF documents or reprints of the relevant content.

5.4 Meta-Analyses

Summarize meta-analyses, indirect treatment comparisons, and network meta-analyses that have been published.

5.5 Non-Clinical Studies

Include studies that do not involve direct patient research, for example research conducted via chart reviews, electronic health/medical records, and administrative claims. Also included in this section are modeling studies and studies that result in non-clinical metrics such as healthcare utilization, economic evidence, and productivity. 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.

Refer to Section 3.0 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 (mean overall costs, cancer-related cost, $/LYG, $/QALY, etc.) 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 3.0 for additional guidance that is relevant for this section, e.g., provide reprints upon request, explain criteria for inclusion and exclusion of studies, etc.

6.0 Supporting Information

6.1 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 upon request, and where possible, provide a link to original sources if they are free.**

6.2 Dossiers and Economic Models

Media: Manufacturers should submit dossiers in an electronic format rather than in print. This will help reduce resource expenditures and improve healthcare system staff's ability to transfer evidence directly into P&T committee submission monographs. **In addition manufacturers must provide a transparent, unlocked copy of the model without a graphical interface.** It should be presented electronically as an Excel workbook, ASCII tab-delimited file or an alternative electronic format that is agreed upon by the requesting organization or its consultants and the manufacturer.

Transparency: The model should be transparent, i.e., designed to allow staff or consultants to investigate the assumptions and calculations, and to perform independent sensitivity analyses by varying individual parameters. **The requesting organization will retain this model for internal analyses and *will not release it to any other party*.** Manuscripts that support the development and reporting of the model should be either attached as appendices or made readily available upon request.

6.3 Product Prescribing Information

Include FDA-approved label, package insert, or prescribing information.

6.4 Patient Information

Include any patient information such as patient package insert (PPI).

6.5 Material Safety Data Sheet

Include Material Safety Data Sheet (MSDS) for product.