

# The AMCP *Format* for Formulary Submissions

Version 4.0

A Format for Submission of Clinical and Economic Evidence  
in Support of Formulary Consideration

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CP

Academy of  
Managed Care  
Pharmacy®

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## PREFACE

The increasing 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.<sup>1,2</sup>

Since its initial release in 2000, the AMCP *Format for Formulary Submissions* has provided a framework to advise drug manufacturers regarding important health care decision maker (HCDM) 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 HCDMs 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 companion diagnostic tests, to name a few. Guidance on logistical matters related to updating dossiers, the challenge of providing pre-approval evidence, and ongoing communication between manufacturers and HCDMs 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. Some sections have significant changes based on the feedback received in the public comment period. For example, Section 3.0 and Section 5.0 provide more clarity on what type of evidence goes into each section.

Lastly, it is important to emphasize that the scope and context of communications between manufacturers and HCDMs should evolve over the product lifecycle as new evidence becomes available. While launch-timed dossiers may rely to a greater extent on modeled projections based on clinical trial evidence and reasonable assumptions related to market dynamics and product uptake, new evidence describing the actual use and effect of the product in a real-world setting should be developed to inform formulary management across the product lifecycle. Ongoing generation of real-world evidence serves the important purpose of further defining and validating claims related to product value. As such, ongoing communication between manufacturers and HCDMs as the value evidence evolves is a critical component to the process.

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<sup>1</sup> 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.

<sup>2</sup> 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 evidence required for evaluating the clinical and economic value of drugs, companion diagnostic 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 opportunity to communicate the value of a product that is grounded in evidence-based medicine principles
- Supporting the FDA’s established 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 health care 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 health care system.

**Second**, the AMCP *Format* streamlines the evidence acquisition and review process for HCDMs and health care 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 health care system staff to formally evaluate the completeness of submissions received and to easily add the results of the HCDM’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 health care 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 health care 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. Approaches to Pharmacy and Therapeutics (P&T) Committee processes and formulary decision making have been reported in the literature.<sup>3,4,5</sup>

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<sup>3</sup> Coalition Working Group (Academy of Managed Care Pharmacy, American Medical Association, American Society of Health-System Pharmacists, Department of Veterans Affairs, National Business Coalition on Health, US Pharmacopeia). Principles of a sound drug formulary. 2000. Available at: <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=9280>. Accessed 1/20/16.

<sup>4</sup> Tyler LS, Cole SW, May JR, et al. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. *Am J Health-Syst Pharm*. 2008;65(13):1272-1283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18589893>. Accessed 1/20/16.

<sup>5</sup> Schiff GD, Galanter WL, Duhig J, et al. A prescription for improving drug formulary decision making. *PLoS Med*. 2012;9(5):1-7. Available at: <http://www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.1001220&representation=PDF>. Accessed 1/20/16.

# GENERAL LOGISTICAL CONSIDERATIONS

## DECISION MAKERS AND MANUFACTURERS

The term “health care decision maker” (HCDM) is used throughout this document to refer to ANY health care personnel, committee, or organization that uses an evidence-based process for making health care coverage and reimbursement decisions 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, clinical practice guideline bodies, and other organized health care 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”.<sup>6</sup> 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.<sup>7</sup>

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 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*.

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<sup>6</sup> 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.

<sup>7</sup> Peretto 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>. Accessed 12/8/15.



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 of drugs and medical devices can respond to unsolicited requests for information about products.<sup>8</sup>

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.

Given the complex regulatory and legal environment, manufacturers should consider and establish their own acceptable rules or policies and procedures on handling unsolicited requests for dossiers. For example, consider policies and procedures to address: 1) What specifically constitutes a request for a dossier versus request for other medical information; 2) How to fulfill requests for dossiers that have multiple indications, or products for which a manufacturer has more than one dossier; and 3) How to handle requests for future updates to dossiers (also see section on Updating Dossiers).

Substantial on-going communication between the HCDM and manufacturer throughout the product evaluation process is critical to manage expectations and maximize the quality of available evidence. When a dossier is requested from a HCDM, 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 HCDM. 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. HCDMs should consider requesting a presentation from or discussion with appropriate manufacturer representatives (e.g., medical personnel, health economists) on specific questions that they may have about the dossier.

HCDMs need and want to know about new product and new indication launches for their planning purposes. Therefore, manufacturers should keep HCDMs 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. Feedback includes dossier completeness, objectiveness, usability, readability, and other user experience of the document, NOT feedback about formulary review status or approval.

## **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

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<sup>8</sup> 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.

appropriate confidentiality agreements between the HCDM and the manufacturer. HCDMs should be aware that the ability of manufacturers to provide complete information is dependent on the recipient to preserve the confidentiality of that information. We note that evidence dossiers submitted to government authorities in the US, the UK, and certain other countries are made available to 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 HCDMs, 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 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.

## 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 HCDMs 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:

- The manufacturer files a supplemental application to the FDA for a new indication; the regulatory decisions should be included in the dossier whether the new indication is approved or denied
- The FDA issues advisory statements about the use of a product, e.g. established a new boxed warning, etc.
- Significant new clinical or economic evidence becomes available, such as:
  - Further support the use of the product for the approved indication
  - Identify patients or sub-populations who should or should not receive the product
  - Demonstrate real world effectiveness and long-term effectiveness
  - Elucidate long-term safety

When updating a dossier, the manufacturer should conduct a complete revision to incorporate new evidence, delete obsolete and less relevant information, and revise content and format in order to keep the dossier concise and relevant. The manufacturer may update the dossier by re-writing a new version of the dossier or amend the existing dossier with a supplemental document that acknowledges new evidence with proper citations, identifies obsolete information in the existing dossier, and describes any additional relevant information to the HCDM. The manufacturer should provide HCDMs with a way to identify newly added information (e.g., highlight revised/new sections or content, describe changes in an appendix, include a summary of changes in a cover letter, 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, dossiers should be evaluated 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 (last completed) 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, or at the discretion of the manufacturer’s policies. While the *Format* does not specify a maximum length of time, the request for updated dossiers should not be indefinite and manufacturers should determine their own policies and procedures. Allowance for this process will avoid HCDMs from having to submit numerous requests for updated information, especially since they may not be aware when updated dossiers may be available. Additionally, the explicitness of the unsolicited request for an updated dossier within a specific time frame will help manufacturers maintain compliance to the unsolicited request process. Whether a manufacturer may *proactively offer* to send an updated dossier(s) to HCDMs at the time of the original unsolicited request for the dossier is at the discretion of the manufacturer.

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 or lost exclusivity. If the manufacturer continues to provide the dossier to requesters, then the status and currency of the dossier 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.

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

## **PAGE LIMITS**

Throughout the *Format*, guidance is provided regarding page limit recommendations for individual sections of a dossier. These recommendations are for general guidance only, as there are many factors that may influence the appropriate section length for a particular product. Within the guidance provided, manufacturers should present relevant evidence and product information as concise and clear as possible to streamline the evidence acquisition and review process. HCDMs have complained about dossiers being too long. Specifically, manufacturers should NOT include overly verbose or superfluous content as a means to meet page limit recommendations.

## DOSSIER INFORMATION BEFORE FDA APPROVAL

It is not uncommon for HCDMs to request a dossier well before FDA approval. In fact, this is one of the most common comments 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. It is understood that it is not possible for manufacturers to provide certain product information or the price of the product before final FDA approval. It is also not the intent for manufacturers to develop two separate dossiers. A manufacturer may choose NOT to develop and provide a dossier before FDA approval or clearance.

To address the HCDMs need to evaluate evidence prior to product approval/clearance, and to assist manufacturers that choose to meet this need, the *Format* offers guidance for providing information before FDA approval/clearance or product launch.

In general, manufacturers have always been able to provide certain information, generally public or published data, regarding a product in late-phase development before FDA approval upon receipt of 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 (sometimes dependent on each manufacturer's policies and procedures).

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" prior to 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 "dossier" may include, but is not limited to:

- 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
- Information from [clinicaltrials.gov](http://clinicaltrials.gov)
- Pre-clinical studies
- Data on file per manufacturer's discretion
- Disease state information, e.g., disease description, epidemiology, clinical presentation, currently available therapies, clinical practice guidelines, etc.
- Pipeline product information, e.g., proposed mechanism of action
- Any other information that a manufacturer deems relevant to the request and allowable according to the manufacturer's policies and procedures
- Some manufacturers may consider providing certain information under a confidentiality agreement

This is not meant to be an exhaustive list. The *Format* intends to provide guidance, however, each manufacturer should consider an approach according to its own policies. Manufacturers should have a clear and consistent process for handling HCDMs' unsolicited requests for "dossiers" prior to FDA approval/clearance.

## **MEDIA FOR DOSSIER AND MODEL SUBMISSIONS**

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

## **IMPLEMENTATION OF VERSION 4.0**

Manufacturers **should** adopt the *Format* Version 4.0 when creating new dossiers after the release of Version 4.0.

For dossier updates after the release of Version 4.0, it is **highly recommended** that manufacturers adopt the *Format* Version 4.0. Manufacturers **should make every effort** to adopt Version 4.0 for dossier updates. However, manufacturers may use discretion based on reasonable factors such as end of product's life cycle, lack of internal resources, etc.

If a manufacturer is in the midst of creating or updating a dossier at the time of this version's release, it is the manufacturer's discretion whether to adopt the *Format* Version 4.0 or to complete the dossier according to Version 3.1.

# SPECIAL CONTENT CONSIDERATIONS

## 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,<sup>9,10</sup> pragmatic clinical trials,<sup>11,12</sup> prospective observational studies,<sup>13</sup> retrospective observational studies,<sup>14</sup> systematic evidence reviews<sup>15,16,17</sup> including indirect treatment comparisons and network meta-analyses,<sup>18</sup> and modeling studies.<sup>19</sup>

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<sup>9</sup> 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>. Accessed 11/26/15.

<sup>10</sup> 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.

<sup>11</sup> 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>. Accessed 11/26/15.

<sup>12</sup> 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>. Accessed 11/26/15.

<sup>13</sup> 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](http://www.ispor.org/taskforces/documents/pos_assesscompeffectivenessgrptfreport.pdf). Accessed 11/26/15.

<sup>14</sup> 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>. Accessed 11/26/15.

<sup>15</sup> 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.

<sup>16</sup> 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](http://www.effectivehealthcare.ahrq.gov). Accessed 11/26/15.

<sup>17</sup> 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.

<sup>18</sup> 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>. Accessed 11/26/15.

<sup>19</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf). Accessed 11/26/15.

For assessing evidence from CER studies, the CER Collaborative ([www.cercollaborative.org](http://www.cercollaborative.org)), formed by AMCP, ISPOR (International Society for Pharmacoeconomics and Outcomes Research) and NPC (National Pharmaceutical Council), developed the CER Tool<sup>20</sup> to assist HCDMs in the evaluation and use of four types of outcomes research: prospective and retrospective observational studies,<sup>21</sup> modeling studies,<sup>22</sup> and indirect treatment comparison studies.<sup>23</sup> HCDMs may also use tools to assess the body of evidence, e.g., Institute for Clinical and Economic Review (ICER) Evidence Rating Matrix,<sup>24,25,26</sup> GRADE.<sup>27,28,29</sup>

## 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 health care 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*. Refer to the following section as well as Section 2.3 for detailed recommendations regarding CDTs.

Additionally, the *Format* can be used to convey evidentiary requirements for medical devices cleared by the FDA. 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.

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. If a medical device manufacturer chooses to use the *Format* to create a device dossier, the manufacturer may indicate “not applicable” for requirements that do not apply to devices. AMCP recognizes the challenge of adapting the *Format* to medical devices without providing explicit requirements and encourages manufacturers to use sound judgment and their own discretion in providing objective information and relevant evidence about a device that will meet the needs of HCDMs.

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<sup>20</sup> CER Collaborative. Comparative Effectiveness Research Tool. Available at:

<https://www.cercollaborative.org/global/default.aspx?RedirectURL=%2fhome%2fdefault.aspx>. Accessed 11/26/15.

<sup>21</sup> 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>. Accessed 11/26/15.

<sup>22</sup> 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>. Accessed 11/26/15.

<sup>23</sup> 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>. Accessed 11/26/15.

<sup>24</sup> Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessment for decision makers. *Med Care*. 2010;48(6):S145-52. Available at: [http://journals.lww.com/lww-medicalcare/Abstract/2010/06001/An\\_Integrated\\_Evidence\\_Rating\\_to\\_Frame\\_Comparative.22.aspx](http://journals.lww.com/lww-medicalcare/Abstract/2010/06001/An_Integrated_Evidence_Rating_to_Frame_Comparative.22.aspx). Accessed 1/20/16

<sup>25</sup> Ollendorf D, Pearson SD. ICER Evidence Rating Matrix: A User's Guide. Available at: <http://www.amcp.org/ICERUserGuide.pdf>.

<sup>26</sup> Synthesizing a Body of Evidence. User Guide and Tool. Available at:

<https://www.cercollaborative.org/modules/module.aspx?ModuleID=10&CTRL=Page&ContentID=2&ContentTypeID=10>. Accessed 1/11/16.

<sup>27</sup> GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926. Accessed 1/11/16.

<sup>28</sup> GRADE 20-part guide. *J Clin Epidemiology*. 2011. Available at: [http://www.gradeworkinggroup.org/publications/JCE\\_series.htm](http://www.gradeworkinggroup.org/publications/JCE_series.htm). Accessed 1/11/16.

<sup>29</sup> U.S. Preventive Services Task Force Procedure Manual. December 2015. Available at:

[http://www.uspreventiveservicestaskforce.org/Home/GetFile/6/301/procedure-manual\\_2015/pdf](http://www.uspreventiveservicestaskforce.org/Home/GetFile/6/301/procedure-manual_2015/pdf). Accessed 1/20/16.

## 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.<sup>30</sup>

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.<sup>31</sup>

The reader is referred to other sources for background information regarding CDTs.<sup>32,33,34</sup> In addition, a number of other CDT evidence gathering and evaluating frameworks have been developed.<sup>35,36,37,38,39</sup>

### 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
- 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

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<sup>30</sup> 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.

<sup>31</sup> 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>. Accessed 11/15/15.

<sup>32</sup> 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.

<sup>33</sup> 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.

<sup>34</sup> 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.

<sup>35</sup> 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.

<sup>36</sup> IOM. Generating evidence for genomic diagnostic test development: workshop summary. 2011. Available at:

[http://www.nap.edu/catalog.php?record\\_id=13133#toc](http://www.nap.edu/catalog.php?record_id=13133#toc). Accessed 7/30/12.

<sup>37</sup> 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.

<sup>38</sup> 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](http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews-Full-Guide_20120530.pdf). Accessed 7/30/12.

<sup>39</sup> Fryback D, Thornbury J. The efficacy of diagnostic imaging. *Med Decis Making*. 1991;11: 88 -94.

<http://www.ncbi.nlm.nih.gov/pubmed/1907710>. Accessed 11/28/15.



and CDT developers may have different responsibilities and processes with regard to evidence submission to HCDMs.

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

- The CDT is co-developed with the drug
  - 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.
- The CDT is developed independently of the drug
  - If the CDT is required in the drug label, the drug manufacturer should, if possible, 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.
  - 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.
- The CDT is developed independently and is targeted for a class of medications
  - The CDT developer should provide a “CDT dossier” that provides information as outlined in this section.

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

## **BIOSIMILARS**

As FDA-approved biosimilars reach the market, HCDMs 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.

A biosimilar has been defined as a biological product that “is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”<sup>40</sup>

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.

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

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<sup>40</sup> 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 11/15/15.

For more information on biosimilars, refer to documents below:

- 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.<sup>41</sup>
- Biologics Price Competition and Innovation Act of 2009 (BPCI Act).<sup>42</sup>
- Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. April 2015.<sup>43</sup>
- Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. April 2015.<sup>44</sup>
- Guidance for Industry: Nonproprietary Naming of Biological Products. Draft Guidance, August 2015.<sup>45</sup>
- Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act. Draft Guidance, August 2014.<sup>46</sup>
- Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Draft Guidance, May 2014.<sup>47</sup>
- Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. April 2015.
- Draft Guidance for Industry: Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. May 2015.<sup>48</sup>

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<sup>41</sup> 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 11/15/15.

<sup>42</sup> 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 11/15/15.

<sup>43</sup> 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 11/15/15.

<sup>44</sup> 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 11/15/15.

<sup>45</sup> 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.

<sup>46</sup> 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 11/15/15.

<sup>47</sup> 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 11/15/15.

<sup>48</sup> 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.

## 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.”<sup>49</sup> 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. Identification of heterogeneity should be noted in Section 2.2.2(4) and the evidence and studies to support it be summarized in Section 3.0 or 5.0, as appropriate. Readers are referred to additional information on heterogeneity of treatment effect.<sup>50,51,52,53</sup>

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<sup>49</sup> 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>.

<sup>50</sup> 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>.

<sup>51</sup> Warholak TL, Hilgaertner JW, Dean JL, et al. Evaluation of an educational program on deciphering heterogeneity for medical coverage decisions. *J Manag Care Pharm.* 2014;20(6):566-73. Available at: <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=18153>. Accessed 1/20/16.

<sup>52</sup> Willke RJ, Zhen Z, Subedi P, et al. From concepts, theory, and evidence of heterogeneity of treatment effect to methodological approaches: a primer. *BMC Med Res Methodol.* 2012;12:185. Available at: <http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-12-185>. Accessed 1/20/16.

<sup>53</sup> Kent DM, Rothwell PM, Ioannidis JP, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials.* 2010;11(1):85. Available at: <http://www.trialsjournal.com/content/pdf/1745-6215-11-85.pdf>. Accessed 1/20/16.

# **EVIDENCE REQUIREMENTS FOR FORMULARY SUBMISSION**

Section 1.0 – Executive Summary

Section 2.0 – Product Information and Disease Description

Section 3.0 – Clinical Evidence

Section 4.0 – Economic Value and Modeling Report

Section 5.0 – Additional Supporting Evidence

Section 6.0 – Dossier Appendices

## **1.0 EXECUTIVE SUMMARY – CLINICAL AND ECONOMIC VALUE OF THE PRODUCT**

The recommended length of Section 1.0 is 5 pages (maximum 8).

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 2.0 through 5.0, and it should be representative of the body of evidence found in Sections 2.0 through 5.0. 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 health care system. Throughout the Executive Summary, the reader should be referred to those places in the full dossier that justify claims and other statements made in the Executive Summary. Hyperlinks to these areas are especially helpful.

### **1.1 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:

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

### **1.2 ECONOMIC BENEFITS**

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

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

Briefly present results of any observational research or economic data, with inclusion of the per member per month (PMPM) or incremental cost effectiveness ratio (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, therapeutic drug monitoring, Risk Evaluation and Mitigation Strategy (REMS) programs, and other administrative offsets that would be above and beyond the cost of the product.

### **1.3 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 2.0 to 5.0 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

The recommended length of Section 2.1 is 5 pages (maximum 10).

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 health care 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 does 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 and ICD-9 codes are also advisable to include for any indications specified in the PI. Inclusion of ICD-9 is to allow retrospective review of claims that contain ICD-9 since conversion to ICD-10 is a recent change (October 2015).
4. The ASP and WAC cost per unit size
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. It may be helpful to include hyperlinks to the relevant off-label sections within the dossier, as well as hyperlinks to [clinicaltrials.gov](http://clinicaltrials.gov) for the new indication studies.
7. Pharmacology
8. Pharmacokinetics/Pharmacodynamics
9. Contraindications/Warnings/Precautions/Adverse Effects
10. Special Populations (e.g., pregnancy, pediatric use, renal impairment, etc.)
11. Interactions with suggestions on how to avoid them
  - Drug/Drug
  - Drug/Food
  - Drug/Disease
12. Dosing and Administration
  - For specialty pharmaceuticals, include any instructions for preparation, administration, and a description of any unique type of delivery devices that do not

- appear in the package insert, as well as information on setting of care. Verbatim language from the package insert should not be supplied here
13. Access, e.g. restrictions on distribution, supply limitations, anticipated shortages, and/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; patient access/assistance contact information
  14. 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. It may be helpful to refer to the PI when determining which therapies would be co-prescribed/used concomitantly.
  15. Describe how product may impact quality measures, e.g., HEDIS scores. 30 day readmissions, CMS Star rating, etc. Include studies that support this information in Section 3.0.

### **2.1.1 PRODUCT COMPARISON**

Concise comparison of PI information with the primary comparator products in the same therapeutic area focused on safety and efficacy and include: dosing, indications, pharmacokinetic/pharmacologic profile, adverse effects, warnings, contraindications, interactions and other relevant characteristics (expand as appropriate for the therapeutic class). The material may include a discussion of comparator 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 3.0 of the dossier.

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

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

## **2.2 PLACE OF THE PRODUCT IN THERAPY**

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

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

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

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

1. Summarize current approaches to treatment including principal therapeutic options (drug and non-drug), common practice patterns, or standards of care; briefly include recommendations supported by well-accepted or nationally recognized clinical practice guidelines and consensus statements, however summarize details of these sources in Section 5.0.
2. Describe the place and anticipated uses of the proposed product for treating disease, especially for certain subpopulations that can be targeted for the use of the product.
3. Indicate the appropriate care 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.
4. Describe heterogeneity of treatment effect, if any, related to the use of the product. Response to therapy may vary from patient to patient. Any information that substantiates heterogeneity effects (benefit and harms) of the proposed therapy should be described here and supported with evidence from studies in Section 3.0 (e.g., cross-over study designs, n-of-1 studies, subgroup analyses, etc.).



5. 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.
6. Describe other product development or post-marketing obligations as required by the FDA such as a 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(5) and note in 2.2.2(6) that the program contains a REMS component.
7. Describe ongoing post-approval monitoring of drug safety and adverse events. Ongoing post-approval monitoring and cost of adverse events for newly approved drugs should be conducted and included. Signals of adverse events indicating disproportional rates of events should be reported. The estimated cost of adverse events, including the cost of monitoring, hospitalizations, emergency room visits, and any other relevant costs associated for treating the adverse event should be included. In addition, the health care decision-maker should contact the drug company for current additional information related to drug safety and adverse events.
8. Describe the expected 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 are linked to disease outcome, e.g. LDL lowering.
9. Other key assumptions and their rationale.

## 2.3 EVIDENCE FOR COMPANION DIAGNOSTIC TESTS<sup>54</sup>

### *Drug Dossier with CDT*

When a CDT has been co-developed with a drug, or when the CDT is required per FDA labeling, then the four elements, analytical validity, clinical validity, clinical utility, and economic value, will generally be captured in the drug dossier. As such, the drug dossier should contain information about the CDT according to Section 2.3.1 and Section 2.3.3.

### *CDT Dossier*

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

#### 2.3.1 PRODUCT INFORMATION FOR CDT

The recommended length of Section 2.3.1 is 5 pages (maximum 10).

1. Generic name, brand name, manufacturer or clinical laboratory
2. Type of test: technical, e.g., immunohistochemical (IHC), fluorescent in situ hybridization (FISH), gene expression profile, etc.
3. Target: describe test target, e.g., biomarker, microarray patten, etc.
4. FDA cleared or approved indication(s)/use(s) with companion drug
5. Date of FDA clearance or approval
6. Intended use: clinical basis for CDT, e.g., diagnosis, prognosis and management, risk management, treatment, monitoring or pre-symptomatic testing
7. Indication and target population(s); prevalence of disease/condition and CDT variant in target population
8. Place of CDT in drug therapy
9. Contraindications, warnings/precautions, interactions relative to CDT use
10. Alternative tests and options available, whether they are CDTs or LDTs; describe relative advantages and disadvantages
11. Other key assumptions and their rationale
12. Supporting clinical and economic evidence for the test, using ACCE framework:
  - Analytical Validity: How well does the test identify the target or marker it is intended to identify?
    - Is the accuracy with which a particular genetic *or* phenotypic characteristic identified within professional standards and federal regulation requirements?
    - Sensitivity: how often is the test positive when the marker is present?
    - Specificity: how often is the test negative when the marker is not present?
    - Accuracy: how often is the test correct?
    - Precision: reproducibility of the test
  - Clinical Validity: How well does the test identify the disease or medical condition of interest?

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<sup>54</sup> Adapted from Guidance for the submission of evidence supporting coverage and reimbursement decisions for medical tests ('The Guidance'), Version 5/12/10, by Josh Carlson, David L Veenstra, Scott D Ramsey, Lou P Garrison, Sean D Sullivan, and Rick Carlson of the University of Washington, with permission.

- 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?
  - Clinical Utility: How does the test improve patient outcomes?
    - Interventions that are based on positive and negative test results
    - Efficacy/effectiveness and safety of the clinical intervention implemented as a result of the test
    - Changes in patient outcomes, treatments received, clinical events, impact on disease progressions, risk-benefit assessment, morbidity, quality of life, survival, etc.
    - Consider inclusion of quantitative risk-benefit decision analytic modeling
  - Economic Value
    - What is the 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 health care services, and health outcomes?
    - The economic analysis should include, among other aspects, the prevalence of the condition, prevalence of the CDT marker of interest, and burden on the patient or health care system to collect and process the biological sample.
    - Include incremental cost per diagnosis, treatment modification, events avoided, life years saved, and quality-adjusted life-years gained, etc.
13. Packaging description, regulatory codes, classification(s), and identifiers
  14. Billing and reimbursement codes, price
  15. Copy of the product label or package insert

### **2.3.2 PLACE OF CDT IN CLINICAL PRACTICE**

The recommended length of Section 2.3.2 is 10 pages (maximum 15).

For stand-alone CDT dossiers, CDT manufacturers or providers should include the following information:

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

### **2.3.3 SUPPORTING CLINICAL DATA FOR CDT**

The recommended length of each study summary is 2 pages (maximum 5). The recommended length of an evidence table row is <1 page (maximum 2) for each study.

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

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

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

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

Evidence in summaries should include:

1. Setting and location of study
2. Study design, Research question(s)
3. Inclusion and exclusion criteria
4. Patient characteristics (demographics, number studied, disease severity, comorbidities)
5. Intervention and control group
6. Patient follow-up procedures (e.g., if an intention-to-treat design is used, were drop-outs followed and for what time period?); Treatment/follow up period
7. Clinical outcome(s) measures
8. Outcomes evaluated
9. Delineate primary vs. secondary study endpoints and their corresponding results
10. Other results/outcomes reported (e.g., quality of life, assay performance)
11. Principal findings
12. Statistical significance of outcomes and power calculations
13. Validation of outcomes instrument (if applicable)
14. Compliance behavior
15. Generalizability of the population treated
16. Relevance to enrolled populations
17. Publication citation(s)/references used
18. 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](http://www.clinicaltrials.gov))

### 3.0 CLINICAL EVIDENCE

Section 3.0 should consist of all clinical studies that support the use and value of the product reported in a clear and concise format. Specifically, the types of studies that should be included in this section are:

1. Prospective clinical studies that investigate any aspect of the product in patients regardless of study design should be included. This includes randomized clinical trials, prospective observational studies, registries, and any other studies that measure clinical endpoints, patient outcomes, or collect information directly from patients. Study results and outcomes include efficacy, effectiveness, comparative efficacy, comparative effectiveness, safety, tolerability, long-term safety, patient preference, patient adherence, patient compliance, patient reported outcomes, quality of life, evidence that identify patient subgroups or clinical setting that may be more appropriate, and other clinically-related outcomes.
2. Retrospective studies supporting the clinical use and clinical value of the product that are conducted using existing data from chart reviews, medical and pharmacy claims, electronic medical records, or other novel sources of data.
3. Studies that synthesize the studies in #1 and #2 above such as indirect treatment comparisons and meta-analyses of the product and/or the primary comparators

Sources of information about the use and value of the product from other sources such as clinical practice guidelines, clinical pathways, previous reviews of product value by HTA agencies, and published systematic reviews by outside academic groups such as the Cochrane Collaborative should go in Section 5.0.

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 HCDM 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, clinical evidence that is relevant for this section includes 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 should 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). If data on off-label use has been submitted to the FDA for the purpose of getting a new indication approved and the FDA decision was to deny the approval of the proposed new indication, then the FDA decision should be briefly summarized.
2. Published and unpublished studies and data
  - Studies available from published journals; medical congress abstracts, posters, and presentations (only when full publications are not available); 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 about clinical outcomes which may include, for example, randomized controlled trials (Phase 2, 3, 4), open-label studies, pragmatic trials, observational or cohort studies, registries, and studies that use adaptive trial designs. See FDA guidance for adaptive trial designs.<sup>55,56</sup>

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<sup>55</sup> FDA. Draft guidance: adaptive design clinical trials for drugs and biologics. February 2010. Available at: <http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf>. Accessed 1/22/16.

- Studies may have one or more study arms
4. Study results regardless of positive, negative, or null findings
  5. US and ex-US studies
  6. Relevant data and findings from the FDA and other US 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 is 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 include, 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.

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<sup>56</sup> FDA. Draft guidance: adaptive designs for medical device clinical studies. May 2015. Available at: <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446729.pdf>. Accessed 1/22/16.

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. One of the most common complaints from HCDMs is that dossiers are too long.

The manufacturer should provide specific journal reprints, copies of congress abstracts, posters, and presentations, and other available study information upon request by HCDMs. All reprint requests may be subject to the Physician Payments Sunshine Act.

For drugs designated by the FDA as “breakthrough drugs” the evidentiary reporting 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**

The recommended length of each study summary is 2 pages (maximum 5).

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

### **3.2 EVIDENCE TABLES**

The recommended length of an evidence table row is <1 page (maximum 2) for each study.

Evidence tables should include the following data elements:

1. Citation, (if unpublished, give abstract information or indicate “data on file”)
2. Treatments
3. Sample size and length of follow-up
4. Inclusion/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

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



## 4.0 ECONOMIC VALUE AND MODELING REPORT

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

### 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 HCDM the risk-benefit tradeoff of the product, and its economic value.

#### 4.1.1 USE OF MODELING FOR DECISION-MAKING

Available data on the clinical benefits and harms and economic impact of the product under consideration are provided in Sections 3.0 and 5.0 of the *Format*, and are the core of evidence-based decision-making. Most of the source data for models are in Section 3.0 whereas Section 5.0 contains data from external sources such as clinical practice guidelines and prior HTAs. These data, however, may have important limitations for decision-making. For example,

1. RCTs may not include all relevant comparator interventions
2. The duration of follow-up in RCTs may be limited
3. RCTs may not have collected all necessary data for economic evaluation
4. Patient populations in RCTs may not be reflective of plan populations
5. Safety data may be limited, or from disparate sources
6. Health care cost impacts may not be generalizable across HCDMs

These limitations have led to recent efforts in comparative effectiveness research to improve the quantity, diversity, and relevance of information available to HCDMs. Comparative effectiveness data – derived from studies including relevant populations, comparators, and outcomes – will prove valuable to HCDMs, and should be reported in Sections 3.0 and 5.0 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 health care 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:

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

Models are not without challenges. In particular, because of the complexity and inherent required assumptions, models can be perceived as a 'black-box' approach or biased. The *Format* has been developed to help address these limitations by providing a consistent

format for conducting and reporting cost-effectiveness models to improve their transparency and acceptability.

Manufacturers should consult with health care system staff, ideally 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.

#### 4.1.2 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 HCDMs. The focus of the *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 health care costs are thus most relevant, and termed in general ‘cost-effectiveness models.’ These models are primarily useful for assessing the overall clinical risk-benefit and economic value of a product in relation to products in its class and other health care interventions in general. There are several specific types of cost-effectiveness models, which are discussed in the Cost-effectiveness Analysis 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 best practices published by ISPOR and Society for Medical Decision Making (SMDM) Modeling Good Research Practices Task Force.<sup>57,58,59,60,61,62,63</sup>

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<sup>57</sup> 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](https://www.ispor.org/workpaper/Modeling_Methods/Model_Parameter_Estimation_and_Uncertainty-6.pdf). Accessed 11/28/15.

<sup>58</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf). Accessed 11/28/15.

<sup>59</sup> 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](http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf). Accessed 11/28/15.

<sup>60</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_using_Discrete_Event_Simulation-4.pdf). Accessed 11/28/15.

<sup>61</sup> 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](https://www.ispor.org/workpaper/Modeling_Methods/Dynamic_Transmission_Modeling-5.pdf). Accessed 11/28/15.

<sup>62</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Conceptualizing_a_Model-2.pdf). Accessed 11/28/15.

<sup>63</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/State-Transition_Modeling-3.pdf). Accessed 11/28/15.

### ***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.”<sup>64</sup> Budget impact models are not intended to establish the overall value of health care 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 HCDMs. These models, as defined here, estimate the target population, drug/product costs, health care cost offsets, and adverse event costs, as well as the expected utilization in the health care system, to derive projected per member per month costs. Budget impact models utilize clinical data and can be relatively complex, and thus should follow the recommendations in this section, and best practices published by ISPOR.<sup>65,66</sup>

### ***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. HCDMs usually have the necessary internal resources to develop such models. Although these models may be useful for negotiations between manufacturers and HCDMs, they are not central to the evidence- and value-based decision making process, and are not addressed further in the *Format*. Financial models are not required, but may be included in the dossier at the discretion of the manufacturer.

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<sup>64</sup> 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>. Accessed 11/28/15.

<sup>65</sup> 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-Budgets\\_Impact\\_analysis.pdf](http://www.ispor.org/workpaper/research_practices/Principles_of_Good_Research_Practices-Budgets_Impact_analysis.pdf). Accessed 11/28/15.

<sup>66</sup> 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>. Accessed 11/28/15.

### 4.1.3 OTHER CONSIDERATIONS

1. A clear, written statement of the decision problem, modeling objective, study perspective, and scope of the model should be developed. This should include: the spectrum of disease considered, target population, alternative interventions, health and other outcomes, and time horizon.
2. ISPOR and SMDM have produced comprehensive guidance related to various aspects of modeling.<sup>67,68,69,70,71,72,73</sup> ISPOR-SMDM best practices should be followed when applicable.
3. When a product is intended for treatment of more than one disease or indication, its impact should be modeled for each, unless a reasonable case can be made for a single model, such as may be the case for budget impact models.
4. Models that have been previously developed may be adapted for use according to the *Format*. An existing model should be modified to follow the general framework described in this document and must be able to demonstrate the system-wide impact of introducing the product to health care system formularies. Evidence supporting the validity of existing models should be provided, as well as sufficient documentation on their design, functioning, and data inputs.
5. Cost-effectiveness analyses conducted alongside RCTs, particularly when of sufficient size and follow-up can provide useful and sometimes substantial evidence of economic value. Cost-effectiveness models should be considered complementary to such studies, allowing for the adjustment of health care resource use, unit costs, effectiveness, and practice patterns.
6. All assumptions should be clearly presented.
7. Specialty pharmaceuticals should generally be addressed similarly to traditional pharmaceutical products. Additional considerations may be required for site of care (e.g. inpatient, home infusion, outpatient infusion center).
8. Due to similarity to their reference product, biosimilars generally do not require the development of specific cost-effectiveness models. Budget impact models or cost-minimization analyses may be more relevant.
9. When possible a standalone, electronic, unlocked, modifiable model should be provided to HCDMs. The use of commonly available software (e.g. Microsoft Excel) is recommended. The model should be interactive and flexible, allowing the user to choose which inputs to include in the model and the ability to tailor inputs to their health system or health plan.

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<sup>67</sup> 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](https://www.ispor.org/workpaper/Modeling_Methods/Model_Parameter_Estimation_and_Uncertainty-6.pdf). Accessed 11/28/15.

<sup>68</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf). Accessed 11/28/15.

<sup>69</sup> 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](http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf). Accessed 11/28/15.

<sup>70</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_using_Discrete_Event_Simulation-4.pdf). Accessed 11/28/15.

<sup>71</sup> 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](https://www.ispor.org/workpaper/Modeling_Methods/Dynamic_Transmission_Modeling-5.pdf). Accessed 1/28/15.

<sup>72</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Conceptualizing_a_Model-2.pdf). Accessed 11/28/15.

<sup>73</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/State-Transition_Modeling-3.pdf). Accessed 11/28/15.

10. 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 HCDM. We recognize the need for flexibility, however. Specific requirements are determined by individual HCDMs, and may consist of data requests or methods beyond those outlined in this document.

## 4.2 COST-EFFECTIVENESS ANALYSIS

### 4.2.1 APPROACH AND FRAMEWORK

#### *Guidelines*

In general, the cost-effectiveness framework should consider recommendations published by ISPOR and SMDM Modeling Good Research Practices Task Force.<sup>74,75,76,77,78,79,80</sup>

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

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

#### *Analytic framework*

The general category of ‘cost-effectiveness’ models includes analyses that value outcomes by assessing clinical events, life expectancy, and/or quality-adjusted life-years (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 health care value, but may be more difficult to interpret from a health care system perspective. It is thus recommended that clinical events, life expectancy, and QALYs all be assessed, with the latter two outcomes primarily relevant for lifetime 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.

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<sup>74</sup> 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](https://www.ispor.org/workpaper/Modeling_Methods/Model_Parameter_Estimation_and_Uncertainty-6.pdf). Accessed 11/28/15.

<sup>75</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_Good_Research_Practices_Overview-1.pdf). Accessed 11/28/15.

<sup>76</sup> 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](http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf). Accessed 11/28/15.

<sup>77</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Modeling_using_Discrete_Event_Simulation-4.pdf). Accessed 11/28/15.

<sup>78</sup> 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](https://www.ispor.org/workpaper/Modeling_Methods/Dynamic_Transmission_Modeling-5.pdf). Accessed 11/28/15.

<sup>79</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/Conceptualizing_a_Model-2.pdf). Accessed 11/28/15.

<sup>80</sup> 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](http://www.ispor.org/workpaper/Modeling_Methods/State-Transition_Modeling-3.pdf). Accessed 11/28/15.

### ***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 Time Frame***

The HCDM 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. The time horizon should be long enough to reflect all important differences in costs and outcomes between the technologies being compared. Adjustment for time preference should be incorporated as appropriate and follow US PHS Panel recommendations (discounting both future costs and health effects).<sup>81</sup>

## **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 well-conducted trials for the treatments of interest. Ideally, comparative trials that evaluate treatments directly should be used. In the absence of such studies, indirect comparisons should be considered. In general, relevant studies should:

1. Directly or indirectly compare and quantify treatment effects and other relevant patient-reported outcomes (including quality of life);
2. Assess patient and community preferences for alternative therapies;
3. Quantify costs and benefits over the natural course of the disease;
4. Assess resources used to support alternative therapies; and
5. 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.

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<sup>81</sup> Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York, NY, Oxford University Press, 1996.

### ***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. The economic impact of treatment-related adverse events should be incorporated into cost-effectiveness analyses. A wide range of estimates should be explored given the challenge of accurately ascertaining the likelihood of low-probability events.

### ***Economic data***

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

### ***Utilities***

Preference estimates should be derived from studies surveying either patients or the general population, using a direct elicitation method or an instrument such as the time-trade off, standard gamble, EQ-5D, HUI, SF-6D, or QWB. Because cost-effectiveness analysis is conducted at the population level, the ideal source of utility values is the general population. This may be impractical in some situations and trial-derived utilities may be used.

### ***Demographic and practice pattern data***

Ideally the model would be interactive, allowing demographic and practice pattern data from the health care 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 health care system staff to evaluate the validity of this approach.

### **4.2.3 CONDUCT**

#### *Base-case estimates*

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

#### *Sensitivity analysis*

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

Both univariate and probabilistic sensitivity analyses should be conducted to provide a more complete picture regarding the robustness of the results. Analysts should justify the distribution used for each parameter that is included in a probabilistic sensitivity analysis. Comprehensive one-way sensitivity analysis of all parameters in the model is also strongly recommended, including assessment of 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 if parameter uncertainty is, at least largely, characterized by random error. The use of tornado diagrams is encouraged to identify the most sensitive parameters. The 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

### 4.3.1 APPROACH AND FRAMEWORK

#### *Guidelines*

The modeling approach and analytic framework of the budget impact model should generally follow the guidance provided by ISPOR.<sup>82,83</sup>

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

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

#### *Perspective and Time Frame*

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

#### *Population*

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

### 4.3.2 DATA SOURCES

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

### 4.3.3 CONDUCT

#### *Results*

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

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<sup>82</sup> 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>. Accessed 11/28/15.

<sup>83</sup> 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-Budget\\_Impact\\_analysis.pdf](http://www.ispor.org/workpaper/research_practices/Principles_of_Good_Research_Practices-Budget_Impact_analysis.pdf). Accessed 11/28/15.

## 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.<sup>84</sup> 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 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, based on the modeling approach being presented.

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

Table 1. Provide a table listing all of the model inputs, including probabilities, costs, and utility estimates if appropriate. Provide a range of values upon which sensitivity analyses are based for each input.

1. Include references in the table for all inputs, including ranges.
2. 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 health care system formulary committees. The following specific data should be presented for each strategy as appropriate for the analysis type:

1. The projected clinical events (e.g., heart attacks, cirrhosis, recurrence)

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<sup>84</sup> 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](http://www.ispor.org/workpaper/modeling_methods/model_transparency_and_validation-7.pdf). Accessed 11/28/15.

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

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

1. Clearly present the model inputs or assumptions that drive the difference in 1) costs, 2) effects, and 3) incremental cost-effectiveness.
2. When appropriate, present 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.<sup>85</sup> This statement provides additional guidance regarding preferred reporting standards for economic evaluations and may serve as an additional resource to model developers.

### **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 user's manual. Interactive models should have the following characteristics:

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

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<sup>85</sup> 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=3D35FD569-431D-8C27-378B8F99EC67>. Accessed 11/28/15.

### ***Model accessibility***

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

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

## **5.0 ADDITIONAL SUPPORTING EVIDENCE**

The recommended length of Section 5.0 is 2 pages (maximum 5) for each study or source.

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), HTAs and systematic reviews (SRs), compendia, 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 US and ex-US 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 position statements, consensus statements, clinical pathways, and other similarly termed guidances 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, if feasible, provide a copy of the full guidelines upon request or provide links to the original guidelines. The manufacturer should describe how it included or excluded clinical practice guidelines in this section.

### **5.2 HEALTH TECHNOLOGY ASSESSMENTS AND SYSTEMATIC REVIEWS**

Summarize relevant HTAs, systematic reviews, and evidence frameworks (also known as value frameworks) that are available. Examples include Cochrane Collaboration systematic reviews, formal systematic reviews published in peer-reviewed journals, evidence reviews by the Agency for Healthcare Research and Quality (AHRQ), Patient-Centered Outcomes Research Institute (PCORI), 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. Since many compendia publications are available only by subscription and are protected by copyrights, manufacturers may not be able to provide PDF documents or reprints of the relevant content, even if requested by HCDMs. Each manufacturer may determine its own process for handling requests for reprints or copies of compendia information.

### **5.4 OTHER ECONOMIC OR OUTCOMES EVIDENCE**

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

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

Refer to Section 3.0 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.

## **5.5 IMPACT ON QUALITY**

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

## **5.6 OTHER EVIDENCE OR INFORMATION**

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

## **6.0 DOSSIER APPENDICES**

### **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 ECONOMIC MODEL(S)**

Include economic model(s).

### **6.3 PRODUCT PRESCRIBING INFORMATION**

Include FDA-approved label, package insert (PI), 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.



## TERMS AND DEFINITIONS

**Biosimilars:** A biosimilar is as a biological product that “is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”<sup>86</sup>

**Budget Impact Models:** A budget impact model (BIM) estimates the expected changes in the expenditure of a health care system after the adoption of a new intervention in a payer-relevant timeframe. BIMs provide a means of synthesizing available knowledge to estimate the likely financial consequences of adopting an intervention, typically from a payer perspective.<sup>87</sup>

**Care pathways:** Care pathways have been used widely in health care, and while definitions vary, care pathways are generally characterized as a method for patient care management that is based on clinical practice guidelines, with the objectives of improving quality of care, reducing variation in clinical practice, and improving the allocation of health care resources.<sup>88</sup>

**Comparative Effectiveness Research (CER):** The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population level.<sup>89</sup>

**Companion Diagnostic Tests:** Companion diagnostic tests have been defined in various ways. The US Food and Drug Administration (FDA) definition describes a CDT as one that provides information that is essential for the safe and effective use of a corresponding therapeutic product.<sup>90</sup> More generally, a CDT is defined as a test that provides information that improves the safety or effectiveness of a drug or biologic. CDTs can be used to:

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

Companion diagnostic tests (both IVDs and medical imaging) may assess the presence of molecular biomarkers including the following forms:

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

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<sup>86</sup> 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 11/15/15.

<sup>87</sup> 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>. Accessed 11/28/15.

<sup>88</sup> Chawla A, Westrich K, Matter S, et al. Care pathways in US healthcare settings: current successes and limitations, and future challenges. *Am J Manag Care*. 2016;22(1):53-62. Available at: [https://ajmc.s3.amazonaws.com/media/pdf/AJMC\\_01\\_2016\\_Chawla%20\(final\).pdf](https://ajmc.s3.amazonaws.com/media/pdf/AJMC_01_2016_Chawla%20(final).pdf). Accessed 1/22/16.

<sup>89</sup> Institute of Medicine. Initial national priorities for comparative effectiveness research. Report Brief. June 2009. Available at: <https://iom.nationalacademies.org/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx>. Accessed 1/22/16.

<sup>90</sup> 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.

**Cost-Benefit Analysis:** An analytical technique derived from economic theory that enumerates and compares the net costs of a health care intervention with the benefits that arise as a consequence of applying that intervention. For this technique, both the net costs and the benefits of the health intervention are expressed in monetary units.<sup>91</sup>

**Cost-Consequence Analysis:** An analytical technique that compares the health intervention of interest to one or more relevant alternatives, listing the cost components and various outcomes of each intervention separately. This type of economic analysis does not indicate the relative importance of the components listed and leaves it to the decision maker to form his or her own view.<sup>90</sup>

**Cost-Effectiveness Analysis:** A systematic method of comparing two or more alternative programs by measuring the costs and consequences of each. A distinguishing feature of cost-effectiveness analysis is that the consequences (health outcomes) of all programs to be compared must be measured in the same common units-natural units related to the clinical objective of the programs (e.g., symptom-free days gained, cases prevented, quality of life years gained).<sup>90</sup>

**Cost-Minimization Analysis:** A type of pharmacoeconomic analysis comparing two alternative therapies only in terms of costs because their outcomes (effectiveness and safety) are found to be or expected to be identical.<sup>90</sup>

**Cost-Utility Analysis:** A specific type of cost-effectiveness analysis that compares two or more alternative choices in terms of both their costs and outcomes, where the outcomes are measured of utility or preference, often as a quality-adjusted life years gained. Cost-utility analysis can be considered the “gold standard” methodology for evaluating the cost-effectiveness of health care choices.<sup>90</sup>

**Decision Analysis:** A quantitative approach to decision making under uncertainty in which all relevant elements of the decision – alternative actions, chance events (along with their probabilities of occurrence), and final consequences – are stated explicitly in a model. Multiple types of data can be incorporated from a variety of sources. This model typically takes the form of a decision tree or an influence diagram and permits the decision maker to determine systematically the relative value of alternative courses of action.<sup>90</sup>

**Decision Tree:** A schematic diagram depicting the logical structure of a choice under conditions of uncertainty, including all relevant alternative decisions available to the decision maker as well as the values and probabilities of all relevant downstream consequences.<sup>90</sup>

**Dossier:** A detailed report (in paper and electronic form) for each product submitted by the manufacturer for consideration that contains (1) clinical and economic data from published and unpublished studies and (2) a disease-based economic model to project the potential impact that introducing the product would have on health and economic consequences occurring across the entire system.

**Effectiveness:** The actual effects of treatment by the drug under "real life" conditions [patients not always remembering to take their doses, physicians often not prescribing the lowest FDA recommended doses, side effects not all controlled, etc]. 'Head to head' effectiveness studies with similar medications are preferable.

**Efficacy:** The potential effects of treatment by the drug under optimal circumstances [e.g. patients all taking their doses at the right times, physicians prescribing FDA recommended doses, side effects appropriately monitored, etc]. Efficacy studies are typically the foundation of new drug submissions to the FDA. Studies that compare the efficacy of similar drugs, rather than just efficacy compared to placebo are preferable.

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<sup>91</sup> Berger ML, Binglefors K, Hedblom EC, Pashos CL, Torrance GW. Health Care Cost, Quality, and Outcomes: ISPOR Book of Terms. Lawrenceville, NJ: ISPOR, 2003.

**Evidence-Based Medicine (EBM):** An approach to health care decision making in which the decision maker is aware of all the relevant evidence and its strengths and weaknesses and is then able to apply that knowledge to decisions. EBM, therefore, consists of clinical expertise and patient preferences combined with critical appraisal of clinical research, with the goal of providing optimal individual patient care. Optimal care thus takes into account patient outcomes and the relative efficiencies among competing alternatives, as demonstrated in the medical literature. This approach to patient care demands that the decision makers' expertise and the appraisal of the clinical evidence base are current and up to date.<sup>92</sup>

**Evidence-Based Medicine – Alternate Definition:** The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.<sup>91</sup>

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

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

**Health Economics:** A discipline that analyses the economic aspects of health and health care and that usually focuses on the costs (inputs) and the consequences (outputs) of health care interventions using methods and theories from economics and medicine.<sup>90</sup>

**Health-Related Quality of Life (HRQOL):** A broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, attitudes, values and perceived levels of satisfaction and general well-being with respect to either specific health conditions or life as a whole from the individual's perspective. (see Patient-Reported Outcomes).<sup>90</sup>

**Incremental Cost Effectiveness Ratio (ICER):** The ICER is a common metric used to evaluate results of cost-effectiveness and cost-utility analyses. The ICER is the difference in costs divided by the difference in outcomes between two comparators.<sup>90</sup>

**Markov Model:** A complex health economics treatment model that describes the natural history of particular diseases, with or without treatment. To capture all critical events, Markov models can categorize health status with a higher level of detail and divide the model's time perspective into finer intervals than is possible with decision trees.<sup>90</sup>

**Model:** In the context of health care evaluation, a model is an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources and whose purpose is to estimate the effects of an intervention on valued health consequences and costs.<sup>93</sup>

**Modeling:** The development of a simplified representation of a system (e.g. population). A particular model may be analytical, visual or both. In pharmacoeconomics specifically or health economics in general, analytical models can be used to pose and answer questions about interventions that cannot be directly answered by clinical trials due to time and financial constraints.<sup>90</sup>

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<sup>92</sup> Sackett DL, Rosenberg WMC, Gray JAM, et al.. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71-72. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2349778/pdf/bmj00524-0009.pdf>. Accessed 1/22/16.

<sup>93</sup> Weinstein MC, O'Brien B et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices – modeling studies. *Value Health*. 2003; 6:9-17. Available at: <http://onlinelibrary.wiley.com/doi/10.1046/j.1524-4733.2003.00234.x/pdf>. Accessed 1/22/16.

**Outcomes Research:** The scientific discipline that evaluates the effect of health care interventions on patient-related, if not patient-specific, clinical, humanistic and economic outcomes. Outcomes research is generally based on the conceptual framework that evaluation of treatment alternatives involves the simultaneous assessment of multiple types of outcomes that are disease-related.<sup>90</sup>

**Patient-Reported Outcomes:** An umbrella term that includes outcome data reported directly by the patient. It is one source of data that may be used to describe a patient's condition and response to treatment. It includes such outcomes as global impressions, functional status, well-being, symptoms, health-related quality of life, satisfaction with treatment and treatment adherence.<sup>90</sup>

**Pharmacoeconomics:** The scientific discipline that assesses the overall value of pharmaceutical health care products, services and programs. Of necessity, it addresses the clinical, humanistic and economic aspects of health care interventions in the prevention, diagnosis, treatment and management of disease. Pharmacoeconomics thus provides information critical to the optimal allocation of health care resources. The field encompasses experts in health economics, risk analysis, technology assessment, clinical evaluation, epidemiology, decision analysis and health services research.<sup>90</sup>

**Quality-Adjusted Life Year (QALY):** A universal health outcome measure applicable to all individuals and all diseases, thereby enabling comparisons across diseases and across programs. A QALY combines, in a single measure, gains or losses in both quantity of life (mortality) and quality of life (morbidity).<sup>90</sup>

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

- No alternate pharmacological or non-pharmacological intervention exists to treat patients with the identified condition;
- The defined condition must be severe, progressive and expected to lead to premature death;
- The defined condition must apply to only a very small number of patients.<sup>94</sup>

**Sensitivity Analysis:** A way to analyze the impact of uncertainty in an economic analysis or a decision (see Decision Analysis, Modeling). The simplest form of sensitivity analysis is a one-way analysis where the value of one variable is changed while keeping the other variables constant, and the impact on results evaluated.<sup>90</sup>

**Specialty Pharmaceuticals:** Within the current version of the *Format*, a product may be considered a specialty pharmaceutical if it requires a difficult or unusual process of delivery to the patient (preparation, handling, storage, inventory, distribution, Risk Evaluation and Mitigation Strategy (REMS) programs, data collection, or administration) or patient management prior to or following administration (monitoring, disease or therapeutic support systems).<sup>95</sup>

**Tornado Diagram:** A set of one-way sensitivity analyses displayed in a single graph, with the most critical variable in terms of impact at the top of the graph and the rest ranked according to their impact thereafter; hence the "tornado" or funnel appearance of the graph.<sup>90</sup>

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<sup>94</sup> Richardson J and McKie J. The rule of rescue. Centre for Health Program Evaluation. Working Paper 112 [Internet] West Heidelberg, Australia. Available at: <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.187.3929&rep=rep1&type=pdf>. Accessed 1/22/16.

<sup>95</sup> AMCP *Format* Addendum: Specialty Pharmaceuticals, December 2012, in AMCP *Format for Formulary Submissions*, Version 3.1. Available at: <http://www.amcp.org/practice-resources/amcp-format-formulary-submissions.pdf>. Accessed 1/22/16.

## **APPENDICES**

- Appendix A: Sample Unsolicited Request Letter
- Appendix B: Formulary Monograph Template

## APPENDIX A: SAMPLE UNSOLICITED REQUEST LETTER

Date

Medical Information/Medical Communications Department

Name of Company

Address

Address

Dear...:

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

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

We consider this unsolicited request to represent the desired information to accompany a formulary submission. Manufacturers should submit a complete dossier well before they expect the product to be considered for formulary review. Our goal is to enable all of the [Organization name] Pharmacy & Therapeutics (P&T) Committees to make evidence-based decisions representing good value for money when selecting preferred treatment options. The AMCP *Format* describes a standardized template for pharmaceutical manufacturers to construct and submit a formulary dossier. The dossier is designed to make the product evaluation process in formulary development more complete, evidence-based and rational.

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

If you require additional information, please call .....

Sincerely,

# APPENDIX B: FORMULARY MONOGRAPH TEMPLATE

## Individual Drug Review

**Generic Name:** [Name]  
**Brand Name:** [Name]  
**Manufacturer:** [Text]  
**Date of Review:** Month Year  
**Reason for Review:** [Text].

### TABLE OF CONTENTS:

*(Click on a link below to view the section.)*

[Executive Summary](#)

[Recommendations](#)

[Key Questions/Issues:](#)

[Issue 1: Efficacy](#)

[Issue 2: Comparative Effectiveness](#)

[Issue 3: Safety](#)

[Issue 4: Value Proposition](#)

[Issue 5: Cost-effective Patient Subgroups](#)

[Clinical Evidence Tables](#)

[Cost-effectiveness Evidence Tables](#)

[Background](#)

[Disease Background](#)

[Pharmacotherapy](#)

[Product Background](#)

[Methodology](#)

[Authorship](#)

[References](#)

### Abbreviations used in this monograph:


## **EXECUTIVE SUMMARY**

### **Key Questions/Issues and Results of Investigation:**

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

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

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

[Text]

*Issue 3: What is the evidence of safety?*

[Text].

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

[Text].

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

[Text]

## **RECOMMENDATIONS TO THE COMMITTEE**

[Summary of findings, key issues & conclusions, 1 or 2 short paragraphs that explain the logic leading to your recommendations.]

Therefore, the following P&T action is recommended:



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

[Narrative summary of evidence for efficacy.]

**ISSUE 2: Is there sufficient evidence to assess real world comparative effectiveness?**

[Narrative summary of evidence for comparative effectiveness.]

**ISSUE 3: What is the evidence of safety?**

[Narrative summary of evidence for safety.]

**ISSUE 4: What is the value proposition for this product?**

**Summary of Product Value**

[Text summary statement]

**Incremental Cost-effectiveness:**

[Discussion of cost-effectiveness analyses]

**Table . Summary of incremental cost-effectiveness ratios found by studies included in this review.**

Cost/QALY (USD)					
Reference					
Setting or Disease 1					
Setting or Disease 2					

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

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



**Table . Validation of instruments used in studies included in this review.**

Name of Instrument	Abbreviation	Description	Numerical Scale	Interpretation of Values	M.I.D.*

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

**Table . Cost-effectiveness evidence summary (Reviewers may change this table format to better fit the economic study methodology)**

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

Abbreviations used in this table: LYS = life-years saved, QALY = quality-adjusted life-year, QOL = quality of life.

## BACKGROUND INFORMATION

### DISEASE BACKGROUND

[Text]

### DISEASE BURDEN

[Text]

### PATHOPHYSIOLOGY

[Text]

## TREATMENT ALTERNATIVES

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

### Preferred Existing Therapy

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

### Other Therapeutic Alternatives

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

## PRODUCT BACKGROUND

### PHARMACOLOGY

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

### PHARMACOKINETICS

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

<b>Route of Administration:</b>	
<b>Bioavailability:</b>	
<b>Time to Peak:</b>	
<b>Multiple dosing:</b>	
<b>Clearance:</b>	

## **ADVERSE EFFECT PROFILE**

[Brief text summary of known side effects and general tolerability from the package insert or other available sources. If clinically important, include a brief table of side effects from the package insert, listing only side effects with incidence rates significantly different from placebo.

This section is for discussion of routine side effects. Major safety issues should be discussed under Issue 3 above.]

## **DRUG INTERACTIONS**

[Text. List these from the package insert. Include a table if appropriate.]

## **METHODOLOGY OF THIS REVIEW**

### **DATABASES SEARCHED:**

Medline

Embase

Cochrane Controlled Trials Registry

Clinicaltrials.gov

Other: [Name]

### **SECONDARY SOURCES:**

Cochrane Reviews Database

BCBSA TEC

NICE

Other: [Name]

### **SEARCH STRATEGY:**

[text]

### **INCLUSION CRITERIA:**

[text]

**Search Results:**

<b>Study Type</b>	<b>N</b>
Randomized controlled trials (RCT)	
Meta-analyses of RCTs	
Systematic reviews	
Randomized pragmatic Trials	
Prospective cohort studies	
Retrospective cohort or case-control studies	
Economic modeling studies	
Case Series	
RCT abstracts, not peer-reviewed	
Other abstracts, posters, etc., not peer-reviewed	

**Articles Excluded from Evidence Synthesis:**

<b>Reason for Exclusion</b>	<b>N</b>

**REVIEW PREPARED BY**

[Author's Name(s), degrees and organization]

**REFERENCES**