The Academy of Managed Care Pharmacy Format for Formulary Submissions: An Evolving Standard—A Foundation for Managed Care Pharmacy Task Force Report

Richard N. Fry, BS, Pharm, Steven G. Avey, RPh, MS, Sean D. Sullivan, PhD

1Foundation for Managed Care Pharmacy, Alexandria, VA, USA; 2Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, WA, USA

ABSTRACT

Objective: The objective of this report is to provide, in detail, the evidentiary requirements contained in Version 2.0 of the Academy of Managed Care Pharmacy’s (AMCP’s) Format for Formulary Submissions and to elaborate on several key issues regarding the use of the Format that users, potential users, and pharmaceutical manufacturers have raised since AMCP published the first version of the guidelines in October 2000.

Background: The AMCP published its Format for Formulary Submissions in October 2000. The AMCP leadership and its members were motivated to develop these guidelines by a growing need to ensure that any increased utilization of medications, biopharmaceuticals, and vaccine products was appropriate and that newer products would bring added clinical and economic value to covered populations. Since publication of the Format, it has garnered nationwide publicity and attracted considerable positive and negative attention. As adoption of the AMCP Format has spread, manufacturers have begun to standardize the framework within which they present population-specific data. Since publication of the AMCP Format, the AMCP and the Foundation for Managed Care Pharmacy (FMCP) have continuously sought input from pharmaceutical manufacturers and health-system pharmacists through various venues to improve and clarify the process. Version 2.0 is the first attempt to address user’s comments and concerns.

Methods: The majority of the article text is taken directly from Version 2.0 of the AMCP Format for Formulary Submissions published by the AMCP in October 2002.

Conclusion: The AMCP and the FMCP believe that the AMCP Format is a tool that will help health systems establish a record of commitment to rational decision making, thus gaining the confidence of patients, clinicians, and members. While providing manufacturers a vehicle for communicating the scientifically based value of their product to a health system, the required evidence to substantiate that value argument allows a pharmacy and therapeutics committee to determine the clinical benefits of a drug, verify any cost savings the drug may generate, and determine the overall cost consequences to their health system. The AMCP Format for Formulary Submissions is an essential tool to evaluate medications, but requires thoughtful consideration as it is used.

Keywords: cost-effectiveness, drug costs, evidence-based medicine, format, formulary, formulary guidelines, formulary submissions, guidelines.

Introduction: Foundation of a Sound Formulary System

Rational product adoption decisions employing clinical, economic, and humanistic data are built on the foundation of a sound formulary system. Newly approved pharmaceutical, biological, and vaccine products should be subjected to a rigorous clinical review and periodic re-review, based on evidence from the clinical literature. Evidence-based assessment of product efficacy, safety, effectiveness, and cost-effectiveness provide the foundation for such a review. These precepts are affirmed by the National Committee for Quality Assurance managed-care organization accreditation standard “Procedures for Pharmaceutical Management” and by the “Principles of a Sound Drug Formulary System” developed and endorsed in August 2000 by the Academy of Managed Care Pharmacy (AMCP) and the Alliance of Community Health Plans, the American Medical Association, the American Society of Health-System Pharmacists, the Department of Veterans Affairs, the Pharmacy Benefit Management
Strategic Healthcare Group, the National Business Coalition on Health, and the U.S. Pharmacopeia [1].

The goal of the formulary review process is to provide a quality pharmaceutical benefit, determined through an evidence-based decision-making process, taking into account the reality of constrained health-care budgets. Where feasible, health systems should make product comparisons relative to existing competitor products as well as to placebo. For products with similar safety and efficacy profiles, they may reasonably make such decisions primarily on net acquisition cost, unless manufacturers can support reasonable product value or other program efficiency arguments with pharmacoeconomic evidence. Cost considerations, in certain circumstances, may be relevant reasons for limiting patient access to certain products. Nevertheless, practices, such as prior authorization, closed formularies, or placing all high-cost products in the highest copayment tier, tend to be highly controversial and are often contested. A brief glossary of terms can be found in Appendix 1.

**Guidelines and Drug Coverage Decisions**

Health-care professionals and health-care systems worldwide are challenged daily to set priorities in an environment where demand for health-care services outweighs the supply of resources allocated to finance it. In the absence of widely accepted models for legitimate and fair priority setting in health care, health-care professionals must rely on the best available evidence to reach consensus about what constitutes a fair allocation of resources to meet competing health-care needs. For example, health-care systems frequently conduct formulary decision making under uncertain conditions owing to the variability of available evidence on safety, effectiveness, and appropriateness of particular interventions. Gibson et al. [2] state, “In the absence of consensus on guiding principles, the problem of priority-setting becomes one of procedural justice—legitimate institutions using fair processes.” Therefore, health systems need tools to support product evaluation and selection with clinical outcomes as the most important consideration, while avoiding the use of low acquisition cost and rebates as the primary basis for selection.

Australia and some European countries have used guidelines requiring pharmaceutical manufacturers to include detailed clinical outcomes and health economic information as part of a formulary submission process since the very early 1990s, and Gold et al. [3] have provided methodologic guidelines for researchers who conduct cost-effectiveness studies. In 1996, Langley and Sullivan proposed a set of guidelines for use by health care systems in the U.S. to obtain useful, comparative, clinical information and economic analysis on pharmaceutical products in order to make sound drug purchasing decisions [4]. Nevertheless, with the exception of guidelines developed by The Regence Group in the United States in 1994, and substantially revised in 1998 [5], no standardized format for the submission of product clinical and economic information by manufacturers existed in America. In an attempt to fill this vacuum, the AMCP published the AMCP Format for Formulary Submissions in October 2000. The AMCP leadership and its members were motivated to develop these guidelines by a growing need to ensure that any increased utilization of medications, biopharmaceuticals, and vaccine products was appropriate and that newer products would bring added clinical and economic value to covered populations. To satisfy this need, the Academy recognized that it had to provide its members with the means to: 1) promote the concept of combining efficacy, safety, effectiveness, and economic evaluation for the formulary decision-making process; 2) provide a consistent and direct means for manufacturers to supply information directly to health systems to support use of their products; and 3) break down cost silos and emphasize that simple acquisition cost reduction is not the best approach to controlling overall health-care expenditures.

Since initial publication of the AMCP Format [6], the Foundation for Managed Care Pharmacy (FMCP) has spearheaded several initiatives to promote its usage. These efforts have included presentations and forums at AMCP and other professional organizations’ national meetings and conferences, articles in newsletters, peer-reviewed and lay literature, and numerous seminars designed to train health-system pharmacists and pharmaceutical industry personnel on the appropriate use of the Format. Consequently, the AMCP Format has garnered nationwide publicity and attracted considerable attention. Adoption of the AMCP Format process by health systems and the pharmaceutical industry has exceeded the AMCP’s and the FMCP’s expectations. Over the past 2 years, a growing grassroots network has developed among health systems stimulating adoption initially by managed health-care systems and pharmacy benefit management company (PBM) and, most recently, by hospitals, integrated health-care systems, state Medicaid agencies, and the Department of Defense. As adoption of the AMCP Format has spread, manufactur-
ers have begun to standardize the framework within which they present population-specific data.

Version 2.0 of the AMCP Format, approved by the AMCP Board of Directors and released in October 2002, is part of an ongoing attempt to issue contemporary standards for evidentiary requirements and to address user comments and concerns. Current and potential users of the AMCP Format will find that the contents sections of the guidelines have not changed substantially. Revision efforts in these sections were focused on providing additional clarity and making the document more user-friendly and understandable. A companion document addresses major areas of concern expressed by health-system pharmacists and the pharmaceutical industry over the past 2 years [7].

The Role of the Format

Formulary submission guidelines support the informed selection of pharmaceuticals, biologicals, and vaccines by standardizing and communicating product and supporting program information requirements, projecting their impact on both the organization and its enrolled patient population, and making evidence and rationale supporting all choice(s) clearer and evaluable by the health-system decision makers. These guidelines emphasize that, whereas cost–benefit analysis and economic modeling are important elements in the value equation, they are secondary to the principal clinical concerns of safety and efficacy.

The AMCP Format’s process is designed to maintain a high standard of objectivity to achieve two important goals. First, it is intended to improve the timeliness, scope, quality, and relevance of information available to a health system’s evaluators and ultimately to its pharmacy and therapeutics (P & T) committees. Nevertheless, health systems should not expect that its use would necessarily improve outcomes or lower drug expenditures. A distinguishing feature of the AMCP Format is its use as an unsolicited request from a health system to a manufacturer for all possible clinical and economic information necessary to assess the overall clinical utility and value that a product brings to a specific patient population and health-care system. In response to this unsolicited request, manufacturers are asked to submit all possible published and unpublished studies and information regarding both Food and Drug Administration (FDA)-approved indications and anticipated off-label uses of the product (permitted under Section 114(a) of the Food and Drug Administration Modernization Act of 1997), should such information exist [8]. Therefore, this request attempts to improve access to material that has been difficult to obtain in the past. It also enables manufacturers to submit such data within regulatory constraints mandated by the FDA. Whereas no explicit FDA guidance regarding unsolicited requests exists, FDA officials have repeatedly stated their intention to issue such guidance in the future. In the meantime, FDA officials have very clearly stated their position that they have responsibility for: 1) assuring that requests for off-label product information are truly unsolicited and unprompted; 2) assuring that the information provided is not false and misleading; and 3) assuring that the response is specific to the requestor.

Further, by assessing the health-system impact of using a product, the data requested can improve the P & T committee’s ability to assess the effects of formulary alternatives on clinical outcomes and economic consequences for the entire health system. Nevertheless, this information still must be weighed in the context of other values such as equity, social justice, the health of individuals as against communities, the “rule of rescue,” and democratic decision making [2,9,10].

Second, the AMCP Format streamlines the data acquisition and review process for health-system staff pharmacists. By clearly specifying the standards of evidence implicit in the existing formulary process, the submission guidelines furnish pharmaceutical manufacturers with consistent direction concerning the nature and format of information that is expected. In addition, the standardized format allows clinical staff to formally evaluate the completeness of submissions received and to easily add the results of the health system’s own literature reviews and analysis. Manufacturers should understand that submission of information in the format recommended does not guarantee approval of their product for formulary listing. Manufacturers and health systems 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 guidelines offer a clear, shared vision of the requirements to facilitate the collaboration necessary between health systems and manufacturers to support drug product evaluation. Recognizing that manufacturers may not have all the requested information, especially for new products, the document describes the minimum information requirements necessary to support a comprehensive assessment of the proposed product.

In response to similar requirements for reimbursement, pricing, and formulary listing in Australia, Canada, the United Kingdom, and other
countries, pharmaceutical manufacturers are already submitting comprehensive reports on the effectiveness, safety, and cost impact of their products [11–14]. The AMCP Format's requirements mirror these requests by requiring manufacturers to provide product dossiers that contain sufficient detail to give transparency to the analytical methods. Although the Format suggests a formalized system, users should view it as a dynamic, rather than static, process. The AMCP and FMCP anticipate that increased standardization of information will lead to progressive improvement in the quality of submissions over time and provide health-system pharmacists with data often unavailable in the past.

The AMCP is not a standard-setting organization. Therefore, the Academy has always viewed the AMCP Format as a template or guide, not a mandate or standard. As such, it does not claim to establish a standard of practice for managed-care pharmacy. It is up to individual health-care systems to decide how they will implement the AMCP Format and how they will operate their formulary review processes. For example, a health system may require dossiers for only new molecular entities. Another may require dossiers for all new products at launch time and for existing products through their annual therapeutic class reviews. Others may choose to provide exceptions to the submission requirements for certain drug classes such as orphan drug products, chemotherapy agents, and HIV/AIDS drugs. Ideally, health systems should only consider products for formulary review when the manufacturer can submit a complete dossier. Realistically, following an unsolicited request from a health system, manufacturers should make every attempt to submit a complete dossier. When evidence is missing, the manufacturer should provide the health system with a detailed explanation of what evidence is missing and a plan that addresses this deficiency within a specific time limit. If a dossier is not submitted following a health system’s unsolicited request, the health system should reserve the right either to refuse to consider the product for formulary admission or to exercise other available options regarding the product’s benefit status that are in keeping with its formulary and drug benefit management policies and procedures.

Role of the Health System

Successful implementation of the AMCP Format process by a health system will include: human, technical (IT), and financial resources to support the process within the plan including support of senior

management and the P & T committee; a commitment by all staff to make it work; clear communication of AMCP Format requirements to pharmaceutical industry representatives; health-system pharmacy staff trained to interpret and integrate the data presented into the formulary process; and accessibility to health-system staff by industry representatives for presentations on data and economic models.

In addition, the health system should provide the manufacturer with timely information regarding dossier submission and product evaluation such as a dossier submission deadline; anticipated date of initial product review or re-evaluation; general demographic information to assist in development of economic analyses, if feasible; notification of additional information or data clarification requirements; and the P & T Committee’s recommendation.

The Manufacturer’s Role

Using the AMCP Format, the pharmaceutical industry will have the opportunity to justify the price of a new agent in terms of its overall value to the health system. In addition, industry scientists and consultants, using a reasonable scientific framework, will have the opportunity to provide additional information (e.g., adherence data, patient satisfaction, indirect and nonmedical cost impacts) to demonstrate the broad value of their products when compared to usual treatments. Therefore, manufacturers have increased responsibility for providing relevant clinical data and economic impact information. The economic data requested must be broadly applicable to a health system’s population and address the systemwide impact of formulary changes on both clinical outcomes and resource utilization and costs. Early planning by manufacturers will help ensure that their product value message is supported by credible evidence. Therefore, it is vital that manufacturers begin a rigorous planning process for drug dossier development during the early stages of Phase III trials. The AMCP Format does not specify methods for economic evaluation. It is the submitter’s responsibility to utilize appropriate techniques and data sources.

Manufacturers should complete their formulary submission dossiers using this AMCP Format to integrate the relevant published and unpublished data evaluating the efficacy, safety, economic impact, and other medical outcomes associated with the use of their product. They should also complete and present Sections 1 through 4 of the
Format’s Evidentiary Requirements in the order listed. Compliance with this reporting format allows for efficient review and facilitates the use of provided information by decision makers. Marked deviations from the AMCP Format may delay the review process. As stated previously, dossiers must provide sufficient detail to give transparency to the analytical methods used; however, the AMCP Format provides considerable flexibility. Where specific sections or data are unavailable or incomplete, the manufacturer should identify the missing data, explain why it is missing, and explain when it will be supplied, if at all. Manufacturers should provide the following additional information: a comprehensive list of references for all studies cited and for information sources from which they drew estimates for use in the economic evaluation; the identity of and contact information for author(s) of the submission document; identity of the author(s) of primary economic evaluations conducted for clinical and disease management intervention strategies; and the identity of a contact person who can answer questions and provide additional information regarding the submission materials for the health-system reviewers.

The Confidentiality Issue

Pharmaceutical companies have repeatedly expressed concern over the ability of health systems to keep proprietary portions of their product dossiers, such as the economic model, confidential. The AMCP has always supported the desire by the pharmaceutical industry to maintain the confidentiality of certain information contained in product dossiers. The most recent version of the AMCP Format contains the following statement: “By submitting this request (the health system) recognizes that confidential information may be provided. (The health system) recognizes the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances.” As public agencies such as state Medicaid agencies and the Department of Defense have begun to adopt the AMCP Format, some pharmaceutical companies have expressed an increasing level of concern about the need for confidentiality. The Academy has counseled public agencies that are considering the use of the AMCP Format to develop procedures that will allow them to keep the dossiers confidential. The Academy strongly recommends that any organization that is using AMCP’s Format should work diligently to find ways to keep the dossiers confidential and examine all opportunities to work within state statutes in meeting this goal. If issues of confidentiality cannot be overcome because of state public disclosure statutes, the information provided by a pharmaceutical manufacturer may not contain sufficient evidence for a public agency to make a rational evidence-based decision regarding the value of the product under consideration. In addition, the AMCP encourages any organization that begins using AMCP’s Format to hold the presubmission meeting with pharmaceutical companies called for in the AMCP Format to disclose the level of confidentiality that will be possible and to ascertain what level of data can be expected to be furnished.

In supporting this concern, it is important to point out that this issue is unique to the United States, because product evaluations are available to the public in Canada, the United Kingdom, and Australia [15]. The concerns in this country seem to revolve around the pharmacoeconomic model, the submission of unpublished studies, and off-label use information and the creation of the dossier itself. While some pharmaceutical companies have spent a great deal of time and money on outcomes research, pharmacoeconomic modeling, and creation of dossiers, others are not as scientifically sophisticated. Because of this broad variation, some pharmaceutical companies would like to keep their work confidential to prevent their competitors from capitalizing on their efforts [7].

Communication: The Key to Success

There should be substantial ongoing communication between the health system and the pharmaceutical company throughout the formulary submission process to manage expectations and maximize the quality of the deliverables. Those organizations that have been early adopters of the AMCP Format have expressed the importance of and concern for good communication. The most common element in the majority of project failures, whether it is from employee performance, the business plan, or vendor relationships, is communication. When a dossier is requested from a health system, it is important for that organization to explain to the pharmaceutical company some basic information, such as their timeline, the evaluation process, potential data sources, any special needs that might exist, etc. This also gives the pharmaceutical company an opportunity to discuss deliverables. If they cannot submit specific studies or provide a certain piece of the economic analysis, it is better to understand the limitations up front.
Again, the AMCP does not presume to dictate to its members that they should significantly alter or disrupt their normal lines of communication with pharmaceutical manufacturers. Nevertheless, both parties should recognize that when there is a high level of collaboration, there is a relative increase in the chances that the process will be smoother and the quality of the dossiers submitted will be higher [7].

Dialogue with the FDA

Because the FDA closely regulates the information a pharmaceutical company can provide regarding their medications, there is apprehension that complying with the AMCP Format information requirements may raise concerns at the FDA. Beginning long before the AMCP Format’s publication, the Academy has maintained an ongoing dialogue with the FDA to keep them apprised of the project’s progress and to seek their guidance. FDA officials have stated on several occasions that they are comfortable with the Academy’s position that the AMCP Format represents an unsolicited request from a health system to a pharmaceutical company for all possible published and unpublished studies and information regarding both FDA-approved indications and anticipated off-label uses of the product. As mentioned earlier, the FDA has three areas of concern relative to this process. First, the information provided cannot be false or misleading. Second, the request must truly be unsolicited. Third, the response must be specific to the requestor.

Regarding the first concern, FDA regulations require pharmaceutical companies to provide accurate information that will benefit the requester. The pharmaceutical industry takes this responsibility seriously, and the AMCP Format recognizes the importance of these requirements. Health systems and manufacturers can virtually eliminate the second and third concerns if they follow some simple procedures. Health systems must initiate the request and clearly identify the information they desire. The AMCP Format is a template designed specifically for this purpose. The AMCP recommends that health systems also submit a signed request letter to accompany the AMCP Format. Pharmaceutical companies must refrain from taking any proactive steps that could be construed as marketing and promotion, such as preparing identical formulary submission documents (dossiers) for a product with the intent of soliciting health-system pharmacist’s requests for the dossiers. In this scenario, the request would not be truly unsolicited nor would the contents of the response (the dossier) be specific to the requestor [7].

Customizing the Economic Model

Some health-care system P & T committee members are under the impression that only pharmacoeconomic models that strictly mirror a health system’s targeted patient population are acceptable. The AMCP Format describes in some detail the most important elements of the requested pharmacoeconomic model. The AMCP Format further stipulates that the economic data called for must be broadly applicable to a health system’s population addressing the systemwide impact of formulary changes on both clinical outcomes and resource utilization and costs. The AMCP Format, however, does not specify methods for economic evaluation. It is the submitter’s responsibility to utilize appropriate techniques and data sources. Ideally, a manufacturer would use a health system’s own data to customize the model. Realistically, a highly individualized model may not be necessary, feasible, or scientifically plausible. Often, the information necessary to create a highly individualized model will not be available because health systems will be either unwilling or unable to supply it. A reasonable compromise may be for the health system to request a model based on national norms or a pre-existing model with the manufacturer justifying the relevance of the data to the health system’s patient population. In addition, the model should be transparent and adaptable, allowing the health system to change multiple elements by inserting its own data. Once a manufacturer receives an unsolicited request letter, it can facilitate this process and avoid misunderstandings by asking the health system to answer a standard set of questions that would detail the information they would be willing to accept, such as national norm data or a pre-existing model. A manufacturer’s dossier that meets a health system’s criteria is more likely to conform to the FDA’s requirements for responses to unsolicited requests [7].

The Importance of Clinical Information

A misconception that has been percolating among potential users of the AMCP Format is that it is merely a tool for presentation of a pharmacoeconomic model. Consequently, health systems that have little expertise in appraising economic models
initially shied away from adopting the guidelines. A careful examination of the AMCP Format document will clearly show that the guidelines, first and foremost, require the health-system staff to perform a thorough clinical evaluation of the medication based on all possible available information obtained from the manufacturer and other sources. If the desired outcome of the medication is not significant or the side effects too onerous, an economic review would be unnecessary. It is imperative to determine the potential clinical impact of a drug on its target patient population before considering the economic consequences.

The field of pharmacoeconomics is relatively new. Therefore, the current number of individuals in this country with a great deal of knowledge and experience in analyzing the type of information required by the AMCP Format is limited. While pharmacoeconomic models and outcomes research have become increasingly accepted as tools for helping health-care systems make formulary decisions, many health systems do not have a pharmacist on staff with sufficient experience to analyze this information. There are at least two solutions to this problem. One would be to acquire pharmacoeconomics training for one or two staff pharmacists. Numerous organizations around the country provide this type of training, including the FMCP. Another solution is to hire an outside consultant to perform the reviews on the pharmacoeconomic modeling. Private consultants, faculty at colleges of pharmacy and experts in the public health arena can help meet health systems’ needs [7].

The Formulary Submission Process

Content

The AMCP Format guidelines do not restrict the content, presentation of data, and the research methods of studies that comprise the dossier. Rather, they specify evidentiary requirements for product review. Nevertheless, in preparation of the evidence, the approach and method adopted by the manufacturer and the techniques employed should be consistent with the formulary evaluation objectives of the health system. The guidelines strongly recommended that the manufacturer consult with the health system’s representatives to determine appropriate sources for data and to agree on specific requirements and model assumptions (Table 1).

Standards of Care and Data Sources

Manufacturers design clinical development programs, in large part, to meet regulatory requirements. When feasible, manufacturers should consider the broader clinical and payer audience who require evidence on new drugs. For example, manufacturers might modify trial designs to reflect comparison products of interest to health systems. Furthermore, economic evaluations should be capable of reflecting the characteristics of the treatment environment of the health system. Analyses based on clinical trials alone or data from other health systems or PBMs may be insufficient unless the manufacturer shows them to be directly applicable to the health system’s membership. The manufacturer should focus on patterns of medical services pro-

<table>
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<th>Table 1: Agenda for presubmission meeting</th>
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<td>A presubmission meeting(s) should take place at least 4 to 6 months before the actual date of anticipated product review to allow time for a manufacturer to gather the necessary data. The meeting(s) will also serve as a forum to discuss the consequences of missing information deemed necessary by the health system. This agenda can serve as a discussion guide to ensure that the health system and the manufacturer address relevant topics. Ongoing communications should occur as deemed necessary.</td>
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<td>Manufacturer representatives should provide a copy of, and be prepared to discuss, the following at the first meeting(s):</td>
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<td><strong>a.</strong> List of intended indications.</td>
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<td><strong>b.</strong> Summary of studies to be included in the formulary submission. This will include:</td>
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<tr>
<td>• Clinical trials (experimental and nonexperimental)</td>
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<td>• Outcomes studies</td>
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<td>• Meta-analysis</td>
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<td>• Retrospective studies</td>
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<td>• Economic and budget impact models</td>
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<td><strong>c.</strong> Use of comparator products and their appropriateness.</td>
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<td><strong>d.</strong> A general description of how the cost and outcomes impact assessments will be developed.</td>
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<td>• List of data sources (studies, databases, etc.)</td>
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<td>• Discuss incorporation of health-system data</td>
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<td>• Discuss conversion of efficacy to effectiveness for both drug and comparators</td>
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<td>• Approach to modeling the health system’s health-care environment</td>
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<td>• Discuss level of patient switching and impact on overall costs</td>
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<td>• Assumptions and suggested approach for determining patient characteristics for switching</td>
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<td><strong>e.</strong> Summary of anticipated studies to be completed within 1–3 years.</td>
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<td><strong>f.</strong> A completed submission checklist (see Table 10).</td>
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vided directly by reasonable peer organizations. In some cases, there may be differences of opinion as to what constitutes appropriate standards of care. This should be resolved with the health system before submission.

**Disclosure of Potential Reporting Bias**

To minimize the potential for bias in formulary submissions, manufacturers should follow generally accepted rules of scientific conduct and reporting of clinical and economic evaluation data [16,17]. At a minimum, the following should be disclosed for economic evaluation studies, budget impact models, and authors of the submission dossier: the identity of all investigators/authors and the details of their affiliations and all financial or contractual relations that might influence the independence of the investigators/authors.

**Recommended Formulary Submission Timeline and Procedures**

**New Products**

The AMCP *Format* recommends the following steps for a submission of new drug products:

**Step 1.** Manufacturers should keep the health-system clinical pharmacy staff informed of the status of drugs in their pipeline. Both parties should identify specific contacts to ensure efficient communication.

Approximately six months before product launch, the health-system pharmacy staff should issue a formal unsolicited request letter that contains a copy of the formulary submission requirements (Table 2). The letter should be addressed to the appropriate company employee who can engage in health professional-to-health professional communication, in compliance with FDA regulations, on provision of label and off-label information.

**Step 2.** Following submission of the unsolicited request, the health-system pharmacy staff and manufacturer representatives may schedule an initial presubmission meeting. In addition to the agenda items listed in Table 1, the two parties should establish a deadline for dossier submission based on the anticipated review date and discuss other pertinent issues such as commercial-in-confidence data, economic model assumptions, and availability of spreadsheet models.

**Step 3.** At least two months before the product review, the manufacturer will present one paper copy and one electronic copy of the submission dossier to the health system.

**Step 4.** The health-system clinical staff assigned to the product will review the submission. Based on the initial review, the manufacturer may be asked to clarify certain points or submit additional information before a formulary monograph is prepared by the health-system staff for P & T review.

**Step 5.** The designated clinical pharmacists will

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**Table 2 Sample unsolicited request letter**

[Date]

[Name of Account Manager/Medical Science Liaison]
[Name of Company]
[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 drug formulary consideration. [Organization name] considers this document an unsolicited request for 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 pharmaceutical products that we consider for formulary inclusion or as part of therapeutic class reviews. The specific details of the [organization name] request have been sent to you previously and are available on the [organization name] Web site ([http://www.xxx.com]).

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 and 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, [organization name] recognizes that confidential information may be provided. [Organization name] recognizes the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances.

Please consider this letter as an unsolicited request for information required by [organization name] for [name of product or products here]. If you require additional information, please call __________.

Sincerely,
prepare a detailed summary (monograph) for P & T review. The summary presents an overview of all data, principal arguments for and against listing the product on formulary, and any conditions that may apply.

**Step 6.** As soon as possible, health-system staff will inform the manufacturer of the P & T committee’s recommendation. Upon request, staff may provide the manufacturer with the rationale for a product’s denial or restriction as well as guidance for reconsideration or appeal.

Note that establishment of a formal appeals process is at the discretion of individual health-care systems. State or federal law may require public entities, such as state Medicaid agencies, the Department of Defense, or the Veterans Administration to have formal appeals processes in place to deal with denials related to formulary decisions.

**Periodic Review of Therapeutic Classes**

Periodically, a health system will undertake reviews of all drugs in each therapeutic class, including drugs currently listed and those that are nonformulary. The health system may ask manufacturers to update their product dossiers with the most recent clinical data and economic modeling information. If P & T committee procedures include a regular therapeutic class review, they should request updated dossiers through issuance of a separate unsolicited request letter. In addition, when a health-system schedules a review of a new competitor product it may ask manufacturers for an updated dossier for products with the same or very similar clinical profiles. In each case, the health system should give manufacturers as much notice as possible.

**Health-System Guidelines for Manufacturers**

(Evidentiary Requirements for Formulary Submission Dossiers)

A complete formulary submission dossier for pharmaceutical, biological, and vaccine products should include the following sections: disease and product information, supporting clinical and economic information, cost-effectiveness and budget impact model report, product value and overall cost, and other supporting information such as reprints, bibliography, checklist, electronic media, and appendices.

**Product Information: Format Section 1.0**

**Product Description (20-Page Limit): Format Section 1.1**

Manufacturers are required to provide detailed information about their product. They should compare the new product with other agents commonly used to treat the condition, whether or not these products are currently on the health system’s formulary. The product description consists of information that manufacturers traditionally incorporate into a product monograph or formulary kit and includes the elements listed in Table 3.

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### Table 3 Product description

- a. Generic, brand name, and therapeutic class of the product.
- b. All dosage forms, including strengths and package sizes.
- c. The National Drug Code (NDC) for all formulations.
- d. A copy of the official product labeling/literature.
- e. The AWP and WAC cost per unit size. (The [—] contract price, if available, should be included as well.)
- f. AHFS or other drug classification.
- g. FDA-approved and other studied indication(s): A detailed discussion of the approved FDA indications and the date approval was granted (or is expected to be granted) must be included. Information on pending off-label indications and other nonlabeled uses, if available, should be included.
- h. Pharmacology.
- i. Pharmacokinetics/pharmacodynamics.
- j. Contraindications.
- k. Warnings/precautions.
- l. Adverse effects.
- m. Interactions, with suggestions on how to avoid them:
  - Drug/drug
  - Drug/food
  - Drug/disease
- n. Dosing and administration.
- o. Access, e.g., restrictions on distribution, supply limitations, anticipated shortages.
- p. Coprescribed/concomitant therapies, including dosages.
- q. Comparison with the pharmacokinetic/pharmacologic profile of other agents in the therapeutic area. The material may include a discussion of comparator product(s) or services for which the proposed product may be expected to substitute or replace (including drug and nondrug interventions). The manufacturer should present this information in tabular form.
Supporting Clinical and Economic Information: Format Section 2.0

Summarizing Key Clinical and Economic Studies: Format Section 2.1

Manufacturers should submit the key clinical and economic studies that have been conducted, whether published or not, for clinical safety, efficacy, economic, and health outcomes evaluations. They should summarize these studies in a clear, concise format. The guidelines strongly encourage the presentation of data from multiple studies in tabular form within a category. All of the elements listed in Table 5 that apply should be included.

Published and Unpublished Clinical Study Results (Two-Page Limit per Study): Format Section 2.2

Manufacturers should provide summaries addressing items a through “m” listed in Table 5 for studies in each of the categories listed in Table 6 (items a–d). The manufacturer should complete evidence tables that summarize the data. Health systems are particularly interested in head-to-head comparison clinical studies between the proposed product and the principal comparators. Summaries of trial results of key comparator products are desirable but not required. Manufacturers should include a discussion of important study findings and comment on their implications for the patient populations represented by the requesting health system. Systematic reviews or meta-analyses may be referenced in Table 6, item “e”. Manufacturers are to include, in the dossier appendix, a reprint of each key study discussed or referenced.

Table 4 Disease description

| a. Epidemiology and relevant risk factors |
| b. Pathophysiology |
| c. Clinical presentation |
| d. Approaches to treatment—principal options/practice patterns |
| e. A description of alternative treatment options (both drug and nondrug) |
| f. The place and anticipated uses of the proposed therapy in treatment (e.g., first line) |
| g. The expected outcomes of therapy |
| h. Other key assumptions and their rationale |

Place of the Product in Therapy (1- to 3-Page Limit): Format Section 1.2

In addition to the disease description, manufacturers should include characteristics of the patients who would be treated for the condition and present a brief summary of information from the literature for each topic. When the manufacturer presents information from studies, it should compile the results in detailed evidence tables. Next, it should attempt to generalize these findings to the populations of the health system and discuss the implications of any differences that exist between the literature and typical practice patterns and patient populations. When more than one disease is addressed, manufacturers are to complete the description for each separate condition. The health system and the manufacturer should determine the relevant treatment options for comparison during the initial presubmission meeting. Specific disease descriptive information should include the elements listed in Table 4 (two- to three-page limit per disease).

Table 5 Study summaries

| All of the following that apply should be included: |
| a. Name of the clinical trial or study, location and study date |
| b. Trial design, randomization and blinding procedures |
| • Research question(s) |
| • Study perspective |
| c. Washout, inclusion and exclusion criteria; |
| d. Sample characteristics (demographics, number studied, disease severity, comorbidities) |
| • Treated population (actual or assumed) |
| e. Patient follow-up procedures (e.g., if an intention-to-treat design is used, were drop-outs followed and for what time period?) |
| • Treatment period |
| f. Treatment and dosage regimens |
| • Treatment framework |
| • Resource utilization classification |
| • Unit costs |
| g. Clinical outcome(s) measures |
| • Outcomes evaluated |
| h. Other outcome measures (e.g., quality of life) |
| • Principal findings |
| i. Statistical significance of outcomes and power calculations |
| j. Validation of outcomes instrument (if applicable) |
| k. Compliance behavior |
| l. Generalizability of the population treated |
| • Relevance to the health system’s enrolled populations |
| m. Publication citation(s)/references used |
In addition, manufacturers should summarize information from all known studies on the product in a spreadsheet format, noting which studies were presented previously (Table 6, items a–e). Evidence table spreadsheets of all published and unpublished trials should follow a standard evidence table format, such as that contained in the AMCP Format’s Appendix C, Template for P & T Monograph, and should include the following data elements:

- Citation, if published
- Treatments
- Sample size
- Inclusion/exclusion criteria
- End points
- Statistical significance
- Study dates
- Results
- Design

Clinical and Disease Management Intervention Strategies (Three-Page Limit): Format Section 2.3
Manufacturers should identify and summarize any proposed ancillary disease or care management intervention strategies that they intend to accompany the product at launch.

Outcomes Studies and Economic Evaluation Supporting Data (Two-Page Limit per Study): Format Section 2.4
Many researchers have expressed concern over the quality of some published economic evaluations [17–19]. Because the focus of this portion of the dossier is a comprehensive assessment of available evidence, manufacturers are not restricted to a specific number of studies by the imposition of methodologic standards. Nevertheless, a health system and/or its consultants are strongly advised to judge the merit of individual studies based on published standards for conducting and reporting these analyses [19–26].

Manufacturers should provide summaries addressing items a through m, as described previously under “Summarizing Key Clinical and Economic Studies: Format Section 2.1,” for all studies in each of the categories listed in Table 7. Health systems are particularly interested in head-to-head comparison studies between the proposed product and the principal comparators. Analyses that focus on actual outcomes rather than intermediate end points are preferred. Although not required, manufacturers are encouraged to supply summaries of principal trial results of key comparator products when these data are referenced or used in economic models. Manufacturers should discuss important study findings and comment on their implications for the health system’s patient population. Manufacturers are to include, in the dossier appendix, a reprint of each key study discussed or referenced.

Modeling Report (20-Page Limit): Format Section 3.0

Model Overview: Format Section 3.1
Properly constructed economic and budget impact models can combine treatment effectiveness, the resources consumed (and costs) by each treatment process, and a measure of uncertainty in any estimates. The goal is to project the health and economic consequences of the health-system formulary changes. Models developed in this manner can aid decisions regarding the addition of a new product to the formulary, help define a product’s specific role, and assist in creating benchmarks against which health systems can measure future product performance. Properly constructed economic and budget impact models should depict the elements detailed in Table 8.

Manufacturers should base their analysis on scientifically appropriate clinical trial, epidemiologic, and economic data. As mentioned earlier, the health
system should be able to modify the model to better reflect practice patterns in their enrolled population. For the analysis and model to be realistic, it may be necessary to include data from the health system, e.g., demographic data. Data derived from expert panels are not generally acceptable, especially for key clinical and treatment pattern variables. Nevertheless, this approach may be understandable for other variables where estimates are not available through literature, databases, trials, or other normal sources.

The model framework should consider recommendations published by the Panel on Cost-Effectiveness in Health and Medicine convened by the US Public Health Service [3]. Although the AMCP Format does not propose a standard model approach, those preparing the product dossiers should always follow good modeling practices. The authors of AMCP’s Format found that models have certain desirable qualities. These qualities are listed in Table 9 and are in no way meant to proscribe model development or impede good scientific design. Rather, the list is intended to provide some guidance to the manufacturer as to those elements of an economic model that are desirable to a health system’s evaluators.

**Parameter Estimates for Models: Format Section 3.2**

Randomized, controlled efficacy studies are required for licensing and registration. These data comprise the foundation for FDA approval, labeled indications, and marketing. Health systems recognize that manufacturers must conduct these studies for the FDA. In addition, health systems are aware that the results observed in randomized trials are likely to represent optimal effects and are difficult to generalize to populations because of patient selection and the close oversight given subjects in clinical trials.

In general, the best quantitative estimates of clinical effectiveness are required, with uncertainty in the estimate(s) handled analytically via sensitivity analysis. Thus, where possible, feasible, and scientifically plausible, scientists preparing the economic model are encouraged to attempt transformation of efficacy results into effectiveness parameters. This may involve inclusion of an adherence parameter into the model or may involve the creative use of retrospective data. Documentation and clear description of the method will be necessary for a health system’s staff to evaluate the validity of this approach.

Manufacturers should consider translation of claims from an efficacy to an effectiveness context when the model’s treatment period extends beyond that represented by the clinical trial; outcomes supported by the trial are intermediate or surrogate in nature; and compliance, dosing, comorbid conditions, and the population of interest (e.g., children, elderly) are expected to differ from the efficacy trial data.

Poor adherence to therapy, especially for chronic conditions, can affect manufacturer claims if they base them exclusively on carefully monitored clini-
cal efficacy trials. All claims promotional or otherwise made for new products should state clearly the assumptions concerning patient adherence. Manufacturers should provide documentation of anticipated adherence patterns from populations similar to the treatment populations of the requesting health system, if available. This may be more plausible for manufacturers who have launched products in other countries before the US introduction.

**Perspective, Time Horizon, and Discounting: Format Section 3.3**

The primary analysis should take the payer perspective. Manufacturers are welcome to take a societal perspective analysis as a secondary evaluation. The analytic model should consider a time horizon that is appropriate to the disease being studied and reflect the decision-making and financial and budget constraints of the health system. When appropriate, adjustment for the time preference should be incorporated and should follow US Public Health Service Panel recommendations [3].

**Analyses: Format Section 3.4**

Analyses should follow accepted approaches for economic models. Transparency and clarity of presentation make for understandable modeling exercises. The requesting health-system staff needs to be able to understand all steps in the modeling process, so researchers are encouraged to spend time thinking about clarity and transparency of results. All assumptions must be presented and justification should be attempted.

A tornado diagram with a comprehensive (all variables) one-way sensitivity analysis is highly recommended. Base-case and other appropriate sensitivity analyses also are recommended. Confidence interval determination, best/worse-case scenario analyses, and net-benefit and acceptability curve estimation are allowable as necessary and appropriate.

When a product is to be used in the treatment of more than one disease, its impact should be modeled for each approved indication, unless a reasonable case can be made for a single model. Because of the complexity involved in constructing a model that simultaneously addresses several indications, manufacturers are advised to prepare a separate model for each condition.

**Presentation of Model Results: Format Section 3.5**

Manufacturers should present model results as follows:

- Present disaggregated results (cost-consequence presentation style) before viewing incremental cost-effectiveness ratios. These data are more easily understood and interpretable by health-system formulary committees.
- Present costs as the total medical and pharmacy costs of introducing the new product and then disaggregate them into various resource components including drug costs.
- Estimates must include the cost of any additional resources associated with implementing the therapy (e.g., disease management).
• Present health effects in disaggregated form before inclusion in a ratio.
• Show sensitivity analyses in tabular or graphical form (tornado diagram), with the base-case results displayed alongside.
• Clearly present factors that drive the cost and cost-effectiveness results, for example, tornado diagrams.

Exceptions: Format Section 3.6
A pre-existing model developed for another health system or for another country may eliminate the need to develop a new model for a particular submission. A model based on national norms may also be acceptable provided the manufacturer submits it in such a manner, such as a spreadsheet, that the health system can either use the default values or insert its own. To be acceptable, the existing model should follow the general framework described in this document and must be able to demonstrate the systemwide impact of introducing the product to the health-system formularies. It is the manufacturer’s responsibility to justify the adequacy of pre-existing models. Developing a model that can be adaptable and allow the health system to make changes in multiple elements will greatly enhance this process.

Product Value and Overall Cost (Two-Page Limit): Format Section 4.0
This section of the submission requirements represents the principal opportunity for a manufacturer to communicate the value of its product to the requesting health-care system. The manufacturer should briefly summarize the information presented previously, state the expected per-unit product cost, and estimate the total pharmacy expenditures for the product. 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 and other outcomes and the economic consequences for the health-care system and its clients and members. This process of redefining the product’s value allows both parties to move beyond mere cost containment to focus on optimizing drug utilization in an environment of limited resources.

Economic Model Media: Format Section 5.2
In addition to the written report, the manufacturer must provide a transparent, unlocked copy of the model without the graphical interface on a 3.5-inch disk or CD ROM as a Microsoft Excel™ workbook, an ASCII tab-delimited file, or an alternative format that is acceptable to the health system or its consultants and the manufacturer. The model should be transparent, i.e., designed to allow staff or consultants to investigate the assumptions and calculations, and to perform independent sensitivity analyses by varying individual parameters. The health-care system will retain product models for internal analyses and will not release them to any other party unless the manufacturer and health-care system reach an agreement to the contrary before submission. Articles and manuscripts that support the development and reporting of the model are to be attached as appendices.

Formulary Submission Checklist: Format Section 5.3
Manufacturers should provide a completed formulary submission checklist (Table 10) with each submission and provide a brief explanation for all missing data.

Barriers to Adoption
Certainly, adoption of the AMCP Format requires a commitment of resources by both health systems and manufacturers. Lack of human, IT, and financial resources to support the process within the plan including support of senior management and the P & T committee is one of the principal barriers to implementation of the Format process. Other barriers to implementation include:

• Lack of expertise in analyzing clinical and health outcomes studies and pharmaco-economic models.
• The misconception that the Format process is merely a tool for presentation of a pharmaco-economic model.
• Mistrust of any economic models prepared by pharmaceutical manufacturers.
• Commitment to a decision-making process based primarily on product cost and rebates (i.e., silo mentality).
• Manufacturer reliance on marketing and promotions to move market share.
• Concern over FDA scrutiny.
• Concern about confidentiality of propriety information contained in dossiers.

Supporting Information: Format Section 5.0
References Contained in Dossiers: Format Section 5.1
A manufacturer’s submissions should list and provide copies of all key clinical and pharmaco-economic references made in sections 2 and 3.
P & T committees could take the easy path and simply put new or expensive drugs on the third tier of their benefit structure and avoid the cost and effort of the AMCP Format process. One of the key purposes of a formulary is to make medications that produce the best positive outcomes at reasonable costs (i.e., those drugs that show value), available to a plan’s membership. The AMCP Format authors designed the guidelines specifically for that purpose. They allow a health system and its P & T committee to determine the clinical benefits of a drug, verify any cost savings the drug may generate, and determine the overall cost consequences to their health system.

If a health system simply puts a new or expensive medication on the third tier, two negative consequences could arise. First, despite its high cost, the medication may have significant clinical value. Providing appropriate incentives for its use could ultimately improve health and possibly lower overall health-care costs. For example, health systems commonly place preferred brand name products in the second copayment tier. For brand name products with no generic equivalents that are known to offer significant clinical and economic benefit for the health system in terms of reduced morbidity, mortality, and reduced hospitalizations and emergency department visits, it may make more sense to add the product to the first tier, generally reserved for generic products. By simply choosing to place the most expensive products on the third tier, a plan can in effect create a disincentive for their members to use them, resulting in missed opportunities to improve the health outcomes for individuals and groups of patients. Second, automatically putting a medication on the third tier denies the P & T committee or other decision-making body the opportunity to fully assess the clinical and economic impact of a product on a health system’s patient population. Paying for a drug that has little or no value can result in unforeseen dire consequences for patients and health systems.

**Conclusion**

The persistent backlash against managed care can be readily attributable to an American culture that is unwilling to accept limits. Writing in *Health Affairs* in 1998, Daniels and Sabin stated, “To change that culture requires a concerted effort at
education, and education requires openness about the rationales for managed care plan’s decisions” [27]. By adhering to careful and thoughtful decision-making processes that provide the rationales for limits, health care systems will be able to show, over time, that “arguably fair decisions are being made and that those making them have established a procedure we should view as legitimate” [27]. The AMCP and FMCP believe that the AMCP Format is a tool that will help health systems establish a record of commitment to rational decision making thus gaining the confidence of patients, clinicians, and members. There is a growing movement toward the use of the AMCP Format for Formulary Submissions as an essential tool to evaluate medications, but its use requires thoughtful consideration.

The successful completion of Version 2.0 of the AMCP Format for Formulary Submissions would not have been possible without the sage advice and constructive comments of the AMCP Format Revision Committee: Kerri Chitwood-Dagner, PharmD, BS Pharm, National Pharmacy Director, Great-West Life; Joseph A. Gricar, MS, Regional Outcomes Research Manager, Pharmacia Corporation; Dell Mather, PharmD, BS Pharm, Senior Director, Pharmacotherapy Assistance and Policy, Prime Therapeutics, Inc.; Marsha Moore, MD, MBA, Senior Vice President, Medical Affairs, AdvancePCS; Pete Penna, PharmD, Partner, Formulary Resources, LLC; and Nancy E. Stalker, PharmD, Vice President of Pharmacy Services, BlueShield of California. The Academy and Foundation are deeply indebted to Dr Sean Sullivan, the principal author of Version 2.0, for his continuing passionate support for the AMCP Format and his tireless devotion to evidence-based decision making.

References

17 Task Force on Principles for Economic Analysis

Appendix 1
Terms and definitions

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 efficacy compared to placebo, are preferable.

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 systems it represents.

Modeling: A quantitative modeling method used to estimate the impact of formulary changes on: 1) potential health outcomes; and 2) total costs of drug and medical care in a population. One possible use of cost and outcomes modeling, for example, is to extrapolate trial-based efficacy data into effectiveness and cost-effectiveness endpoints of relevance to health-care systems. Cost and outcomes impact data from models can then be used to assess the health and overall fiscal consequences of formulary changes.