

Incorporating Clinical Outcomes and Economic Consequences into Drug Formulary Decisions: A Practical Approach

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Abstract

Background: In 1994, Regence BlueShield (Regence), a large non-staff model health plan, adopted guidelines governing the review of new and existing drug products. However, certain limitations were apparent: adequate data were not available in a timely fashion; unpublished studies and information on unapproved indications were difficult to obtain; data addressing humanistic and economic outcomes were not routinely supplied by manufacturers; and the time required by Regence staff clinical pharmacists to assemble and summarize published clinical studies for the pharmacy and therapeutics (P&T) committee was excessive.

Objective: To describe the process used by Regence to collect and review clinical, economic, and other health outcomes data as part of the plan's drug formulary adoption process.

Process Description: To address these limitations, Regence revised its process to require pharmaceutical manufacturers to submit a detailed dossier with clinical and economic data from published and unpublished studies, along with a disease-based economic model projecting the potential impact that

introducing the product would have on health outcomes and economic consequences occurring across the entire Regence system. After performing independent literature reviews to ensure the accuracy and comprehensiveness of the information obtained, clinical pharmacists at Regence complete a detailed summary of each drug for the P&T committee.

Conclusion: The new process has addressed the limitations of the previous system and, by improving the timeliness and relevance of available information, it supports Regence's goal of maintaining an evidence-based formulary.

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For editorial comment, see page 356.

One of the most vexing problems facing drug formulary committees and the health plans that operate them relates to the criteria and data used to make approval or removal decisions from the limited list. If agents are selected for the formulary with clinical outcomes as the primary consideration, the formulary can be an effective management tool with good acceptance by the provider community. If, however, formulary products are selected primarily on the basis of rebates and low acquisition cost, the health system may experience higher overall costs and the pharmacy benefit may be sharply criticized by health plan providers, enrollees, and suppliers wishing to see their products listed.

The purpose of this paper is to describe the process used by a large non-staff model health plan (Regence BlueShield) to collect and review clinical, economic, and other health outcomes data as part of

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the plan's drug formulary adoption process. We begin by describing the general operating principles adopted in 1994 that guide Regence clinical staff and the pharmacy and therapeutics (P&T) committee. Next we highlight limitations associated with this process that prompted a revision in 1998. We provide a detailed description of the revised guidelines and implications of their use. Finally, we supply a brief summary of our preliminary experience with the new process and our expectations for the future.

... THE REGENCE FORMULARY ...

Regence BlueShield (Regence) is the largest managed health plan in the state of Washington. It is a non-staff model plan, with more than 10,000 physicians contracted and more than 800 participating pharmacies. In 1998 Regence covered more than 1.1 million lives and provided pharmacy benefits through a prescription card program to more than 900,000 enrollees.

Regence manages its pharmacy program and formulary with a team of clinical pharmacists, supported by claims processing and data reporting services from Diversified Pharmaceutical Services. The drug formulary provides the basis for pharmaceutical care for its members and includes not only a list of covered products, but also clinical guidelines governing their use. In 1994, Regence adopted guidelines governing the review of new and existing drug products (Table 1). For each product, formulary decisions are supported by an extensive clinical review of safety, efficacy, and, when available, effectiveness data. All formulary decisions are made by an external P&T committee of leading Washington physicians and clinical pharmacists.

The Regence review and approval process has been designed to maintain a high standard of objectivity: an external P&T committee composed of local clinical leaders; strict, evidence-based standards for formulary review; no votes by Regence staff (staff are not even allowed to own drug company stock); and rebates returned entirely to employer groups (thereby reducing the influence of rebates on the formulary decision-making process).

... THE FORMULARY REVIEW PROCESS:
PRIOR GUIDELINES ...

Table 1. Regence BlueShield Formulary Guidelines (Adopted 1994, Revised 1998)

<ol style="list-style-type: none">1. Regence clinical pharmacists complete a detailed review of each drug, based on the clinical literature. All drugs in a therapeutic class are reviewed at least every other year.2. The medical literature regarding the efficacy, effectiveness, and relative safety of medications is the foundation for formulary review.3. Food and Drug Administration "AB" rated generics will generally be preferred.4. Brand name products are included only when they offer value to our subscribers (eg, significantly more clinically effective than generics or other brands in the same therapeutic class).5. When clinical studies have shown that several drugs are clinically equivalent, only the products with the lowest net cost will be included in the formulary.6. Improved dosage forms are considered only when their cost effectiveness can be documented.7. For each drug under review, manufacturers will be required to submit dossiers that include detailed clinical and economic information, including data from published and unpublished studies, and outcomes modeling (<i>added in 1998</i>).8. Economic modeling will be used to evaluate the impact of each drug on patients' clinical outcomes, medical claims, and costs of care (<i>added in 1998</i>).
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The 1994 guidelines provided the necessary framework for the clinical evaluation of drug products. However, the following limitations were apparent:

1. Adequate data concerning the safety and efficacy of drug products were not available at the time of formulary review. Regence wants to use an evidence-based approach to selecting drug products for the formulary. However, evidence-based assessments of new products are difficult to achieve when very few studies are available at the time of formulary approval. Recently, the Food and Drug Administration (FDA) accelerated the review process for drugs deemed "life saving." One important consequence of this process, however, is that there are even fewer studies available for formulary evaluation.
2. Unpublished studies and studies on unapproved indications were not accessible or required a specific request from Regence to be released by the manufacturer. These data often are instructive to health plans because they can provide more precise information to project expected patterns of use and cost. Health plans can get summary data from the FDA and some clinical studies from the

manufacturer, but not all data are judged “releasable” to the health plan.

3. Manufacturers did not uniformly supply information on quality-of-life, functional-status, and cost-effectiveness studies. In part, this may be due to the manufacturers’ belief that health plans do not desire the information or will question its relevance to their own institutions and patient populations. More importantly, we believe that health economics information exchange between manufacturers and Regence may have been unnecessarily restricted by the Division of Drug Marketing, Advertising and Communications (DDMAC) of the FDA. DDMAC has publicly stated on many occasions that they frown on the use of health economics information that is based on modeling of disease states, treatment pathways, and clinical and economic consequences not established in randomized controlled trials. Regence needed to establish a method for requesting such information that was not in conflict with the FDA, yet enabled the acquisition of data that could be useful in the formulary process.
4. Time required by Regence staff clinical pharmacists to assemble and summarize published clinical studies for the P&T committee was excessive. During the past several years, manufacturers had been preparing a formulary kit that contained clinical and promotional materials for distribution to health plans. We felt that Regence needed to provide guidance to manufacturers on the content, quality, and quantity of information contained in the formulary kit and, thus, potentially reduce duplication of effort by Regence staff.

... THE FORMULARY REVIEW PROCESS:
CURRENT GUIDELINES ...

Working with faculty from the University of Washington, Regence revised the formulary review process in 1998 to address the limitations of the 1994 guidelines. As a template, Regence chose to use a set of guidelines proposed by Langley and Sullivan describing the use of pharmacoeconomic data by managed care plans.¹ For each new product, the 1998 guidelines now require pharmaceutical manufacturers to submit a detailed dossier 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 outcomes and economic consequences occurring across the entire Regence system (ie, both medical and pharmacy costs).

The Regence P&T committee approved the first version of the “Guidelines for the Submission of Clinical and Economic Data Supporting Formulary Consideration” in June 1997. The guidelines became effective in January 1998.

... SUBMISSION DOSSIER ...

Under the 1998 guidelines, manufacturers are required to submit a dossier for each new product. In addition, submissions may be required during periodic therapeutic-class reviews. Figure 1 displays the interrelated categories of data to be addressed by each submission. This flow of information converges to provide an estimate of the product’s overall safety, efficacy, and cost in the Regence environment. After performing independent literature reviews to ensure the accuracy and comprehensiveness of the information obtained, clinical pharmacists at Regence complete a detailed summary of each drug for the P&T committee.

The revised process serves to enhance, rather than to replace, the formalized review and assessment process already used by Regence staff and the P&T committee. By requiring submission of a dossier, the new system places the onus on drug manufacturers to make a case for each product based on sound clinical and economic evidence and outcomes modeling specific for the Regence patient population. Placing the burden of proof on the intervention is consistent with an evidence-based decision-making process and has been advocated by others.³⁻⁵

The submission dossier contains 7 sections under 4 main headings:

- Information elements
- Modeling
- Disclosure of the potential for bias
- Summary of product clinical value and overall cost

Information Elements

Regence is committed to the principles of evidence-based medicine⁶ as the foundation for formulary decisions. By establishing a standardized format for key data, Regence clinical staff can much more easily complete their own independent reviews. The primary focus is not on the quantity of information obtained. Regence has established limits on the amount of information presented in each section in order to give detailed consideration to the most rigorous and relevant data.

Disease Description

- Provide a summary of the epidemiology of each disease or condition in which the new therapy will be used, highlighting incidence, prevalence, and relevant risk factors.
- Describe the pathophysiology, clinical presentation, and principal treatment options, stressing any effect the new therapy will have on therapeutic guidelines or existing disease management programs used by Regence.

Applicants must provide a thorough summary of the current knowledge of the incidence and prevalence of the disease states in which the new therapy will be used. Relevant risk factors for the development of these conditions also should be described. Attempts should be made to generalize the findings of epidemiologic studies to the Regence patient population. Any implications arising from differences between the characteristics of the populations reported in epidemiologic studies and the Regence population should be addressed.

A summary of current knowledge regarding the pathophysiology and clinical presentation of the dis-

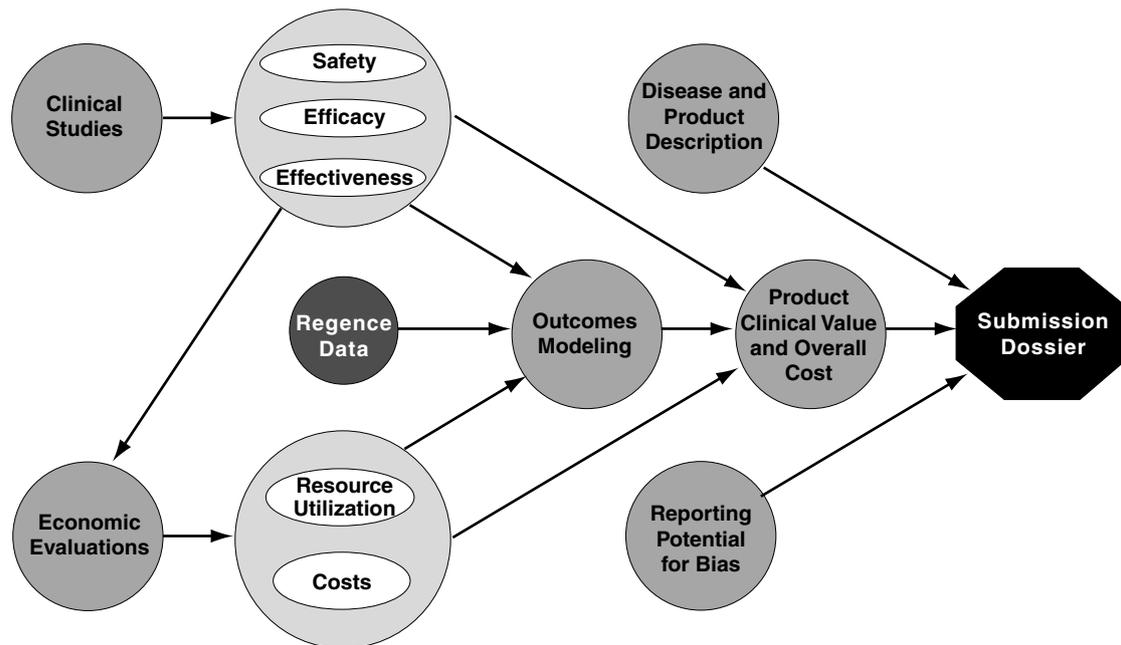
ease or condition also should be provided. Principal options and patterns of treatment currently used by the medical community should be described. In addition, the applicant should illustrate any scenarios in which the new therapy would affect disease management programs that Regence currently has in place.

Product Description

- Provide a description of the product using the format of a brief drug monograph.
- Compare and contrast the pharmacologic/pharmacokinetic profile of the new therapy with that of other agents in the therapeutic class.

A detailed description of product characteristics should also be provided. In most cases, information from FDA-approved labeling will suffice for the product description. However, Regence also asks that the applicant draw comparisons with the pharmacologic and pharmacokinetic profiles of other products in the therapeutic area regardless of their status on the Regence formulary. The required information is outlined in Table 2.

Figure 1. Interrelationship and Flow of Elements in the Submission Dossier



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Clinical Studies

- Provide brief descriptions of studies from the following categories: pivotal safety and efficacy trials, prospective effectiveness trials, trials reporting other noneconomic endpoints such as health status measures or health-related quality of life, and retrospective studies.
- Reference relevant review articles and meta-analyses.
- Present a spreadsheet summary of all known clinical trials.

Brief (1-page) descriptions of up to 5 important published or unpublished studies from each category should be presented. They should highlight key elements of the study design, sample selection, and study findings. The generalizability of study findings and their implications for the Regence patient population also should be addressed. A reprint or copy of each study considered from these areas should be attached in an appendix. Meta-analyses or review articles that provide pertinent comprehensive and unbiased clinical information also can be referenced in this section, and a copy or reprint of each should be included in an appendix.

Although Regence seeks information from all known clinical trials involving the product, an in-depth summary of each would be a burdensome and unnecessary requirement. For this reason, a spreadsheet format should be used to report information from all known published and unpublished clinical studies, including those for which a 1-page description has been submitted. The spreadsheet should address a variety of factors including important study characteristics, methodological issues, and findings. Citations also should be provided for all published studies. Sufficient information should be presented to allow Regence to grade the quality of the evidence for each study.

Economic Evaluations

- Provide brief descriptions of studies from the following categories: cost-efficacy studies, cost-effectiveness studies, and cross-sectional or retrospective economic evaluations.
- Reference relevant review articles and meta-analyses.
- Present a spreadsheet summary of all known economic evaluations.

Once again, brief descriptions of up to 5 notable published or unpublished studies from each category should be provided, and copies or reprints should be attached in an appendix. Study summaries should be no more than 2 pages in length

and should address important study elements as well as the generalizability of the findings and their implications for the Regence patient population.

Some concern has been expressed regarding the quality of economic evaluations of pharmaceutical products.⁷⁻¹⁰ Methodological inconsistencies and potential sources of bias can lead to errant conclusions or findings that have limited generalizability. Regence is aware of these limitations and uses published standards governing the conduct and reporting of these analyses to determine the merit of individual studies.^{11,12} However, because a comprehensive assessment of all available evidence is emphasized here, Regence will not impose strict methodological criteria to limit the number of studies reported. In view of the variety of methods, techniques, and assumptions that can be used in economic analyses, the importance of clarity and transparency in the presentation of study design, analysis, and results cannot be overemphasized.

Applicable review articles should be referenced and attached in an appendix. As in the previous section, a spreadsheet summary should be constructed that lists key factors from an exhaustive listing of all known economic analyses involving the product. Sufficient details should be provided to support evidence grading, and citations of all published studies should be supplied.

Table 2. Product Information Required by Regence BlueShield

<ul style="list-style-type: none"> • American Hospital Formulary Service drug classification (if applicable) • FDA-approved indications • Anticipated off-label uses • Pharmacology • Pharmacokinetics • Contraindications • Warnings and precautions • Adverse effects • Interactions (drug-drug, drug-food, drug-disease) • National Drug Code numbers of all available dosage forms • Dosing and administration • Comparison with the pharmacokinetic/pharmacologic profile of other agents in the therapeutic classification
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Modeling

- A disease-based economic model demonstrating the system-wide impact of introducing the product to Regence's formulary should be constructed.
- The model should be flexibly designed to incorporate Regence-specific data to estimate the impact of the agent on clinical outcomes and resource utilization after introduction of the product.
- In addition to a detailed report describing the model's structure and findings, a transparent, unlocked electronic version of the model (without graphical interface) should be provided to allow Regence to perform its own sensitivity analyses on key parameters.
- The use of pre-existing models to fulfill the requirements of this section must be justified.

Although it is impossible to project a product's overall impact with absolute accuracy and precision, reasonable estimates can be obtained through the process of economic modeling. Economic models can provide a framework for classifying and combining various forms of existing data concerning treatment processes, outcomes, and costs to yield a simplified representation of the real-world consequences of formulary alterations.

When the data necessary to answer an important question are inadequate or unavailable, meaningful information still can be derived from these models. Results from previous analyses can be extended to different settings, patient populations, or time periods. Intermediate measures can be transformed to final outcomes. For instance, serum cholesterol con-

centrations can be used to predict a product's impact on the incidence of myocardial infarctions or survival rates in a given patient population.

Through sensitivity analyses, the effects of changes in rates or quantities of key parameters can provide a measure of the uncertainty in existing data. Input parameters, such as estimates of effectiveness or resource utilization, can be systematically varied to examine expected outcomes in a broad range of real-world scenarios. Conversely, an important outcome or consequence can be fixed at a certain level and then used to determine the necessary range of rates, quantities, or costs that would be required to produce it.

Although specific formats may vary, each model should incorporate a disease-based treatment framework. By moving beyond simple drug-to-drug comparisons, disease-based models can link estimates of the effectiveness of multiple treatments, the resources expended by each treatment process, and a measure of uncertainty in these estimates to project the overall impact on health and economic outcomes due to specific alterations in the Regence formulary.

Properly constructed economic models identify key parameters and define their flexibly to allow the incorporation of Regence-specific data. These parameters are listed in Table 3. Regence can supply some of the information required to support this process and should be consulted in the early stages of model development to discuss data availability.

Analyses should be performed to examine 2 different scenarios. First, an analysis should be performed to examine the total current costs occurring in the Regence system for the disease area in which the product is to be used. Next, a scenario should be modeled in which the product has been listed on the Regence formulary and a new equilibrium of outcomes and resource utilization has been reached. For this second scenario, analysts must anticipate patterns and rates of drug substitution after the addition of the new product. The model can then reflect the system-wide impact of using the product by identifying the subsequent redistribution of patients and resources among the various treatment processes.

Selecting appropriate comparator products is an important step in the modeling process. Because the Regence formulary typically lists a limited number of agents in each therapeutic area, models do not need to accommodate an exhaustive list of therapies. For example, a model for a new hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor would not necessarily need to

Table 3. Parameters Included in Properly Constructed Economic Models for Regence BlueShield

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| <ul style="list-style-type: none"> • Natural history, clinical course, and outcomes of the disease or condition • Primary treatment options and the process of treatment for each option (reflecting any clinical guidelines or pathways used by Regence BlueShield) • Proportion and characteristics of individuals by treatment process • Resources used to support each treatment process • Costs of the resources used for each treatment process • Outcomes of therapy for each treatment process* |
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*Treatment outcomes should include clinical outcomes, adverse events, and health-related quality-of-life measures.

include 2 of the 5 currently marketed products, because they are not on the Regence formulary. Submitting companies are urged to consult with the Regence formulary editor early in the development process to receive assistance in the determination of appropriate comparator products and modeled outcomes.

Regence acknowledges that a particular modeling approach will not be appropriate for all drugs or diseases. However, the model's framework should reflect careful consideration of published guidelines or recommendations, such as those developed by the Panel on Cost-Effectiveness in Health and Medicine.¹² Results obtained from the modeling process will be most useful when models are characterized by the elements listed in Table 4.

Regence will use guidelines recently published by the *British Medical Journal*¹¹ to assist its evaluation of the content and quality of submissions. The following information should be reported in tabular form: total resource utilization, total costs, total effectiveness, incremental costs, and incremental effectiveness. When possible, total and incremental effectiveness measures should be reported in both natural units and quality-adjusted life years. In addition to this written report, an unlocked, electronic version of the model without graphical interface should be provided. This will permit Regence to investigate underlying assumptions, confirm calculations, and perform sensitivity analyses on important parameters.

In certain situations, a new model will not need to be developed because an existing model follows the general structure described herein and can demonstrate the system-wide impact of adding the product to Regence's formulary. The submitting company is responsible for justifying the adequacy of pre-existing models.

Many may question the validity of a modeling process that relies on assumptions and estimates from various sources to project the overall implications of formulary alterations. Indeed, the complexity of economic models may lend scientific credence to inappropriate decisions. However, when interpreted in the proper context, results from modeling analyses can aid decision making by increasing the quantity of available information and by identifying areas in which information is lacking.

Disclosure of the Potential for Bias

- For each economic analysis, provide full disclosure of investigators' identities, any financial

relationships between the sponsoring firm and the investigators, and the degree to which investigators were afforded independence in the design and methodology of the study, as well as rights to publish the results.

Economic analyses are often viewed by manufacturers as being an integral component of their marketing strategy. Therefore, the incentive to produce and disseminate only the most favorable findings is substantial. This incentive heightens the potential for bias and has led to considerable skepticism regarding the scientific validity and objectivity of industry-sponsored research.^{7,9,13}

To address the potential for bias in economic analyses, Regence BlueShield requires that for each reported analysis, full disclosure be made as to the identity of the investigators, any financial relationships between the sponsoring firm and the investigators, the extent to which investigators were afforded independence, and the degree to which investigators were allowed rights to publish the results of their analyses.

Summary of Product Clinical Value and Overall Cost

- Information presented in the previous sections should be briefly summarized.
- Anticipated product expenditures should be justified in terms of the expected health outcomes and

Table 4. Model Characteristics Considered Most Useful by Regence BlueShield

- Highlighting of key assumptions and justification of their use
- Listing the source of parameter estimates
- Modification of data to reflect the effectiveness, rather than the efficacy, of each treatment process
- Incorporation of final outcomes or demonstration of a link between intermediate and final outcomes
- Separation of the volume of resources utilized and the direct medical unit costs for each resource
- Projection of the product's impact over an appropriate time period and justification of the time horizon chosen
- Performance of incremental cost-effectiveness analyses, incorporating patient preferences for treatment outcomes when possible
- Performance of sensitivity analyses on pivotal estimates and assumptions

their associated economic consequences in the Regence environment.

The final section of the submission requirements represents the principal opportunity for a manufacturer to communicate the value of its product in the Regence environment. The company should briefly summarize the information presented, state the expected per unit product cost, and estimate Regence's annual expenditures for the product. Based on this information, a value argument should then be articulated to justify expenditures on this product in the context of its anticipated effects on clinical and health-related quality-of-life outcomes and their economic consequences for the Regence plan and its clients and members.

... DISCUSSION ...

A recent survey demonstrates that the individuals who make formulary decisions, the types of information they consider, and the manner in which a final decision is reached may differ widely across health plans.¹⁴ Regence revised its formulary review process in 1998 to address specific limitations that had been identified. By requiring a submission dossier and outcomes modeling for all new products, the 1998 guidelines will achieve 2 important goals.

First, the timeliness, scope, quality, and relevance of information available to the P&T committee will likely be improved. The requirement of submitting unpublished studies and information regarding anticipated off-label uses of the product improves access to material that has been difficult to obtain in the past. It also enables manufacturers to submit such data within FDA regulatory constraints. In a similar manner, the addition of disease-based clinical and economic modeling incorporating Regence-specific data may enable a better assessment of the overall impact of introducing the product to Regence's formulary. Results from models of this nature can be used to aid decisions regarding formulary additions, assist in clarifying a product's specific role, and support the establishment of performance benchmarks against which a product's performance can be periodically measured. These models can improve the P&T committee's ability to move beyond the acquisition cost of pharmaceuticals to the more relevant issue of the effects of formulary alterations on clinical outcomes and economic consequences for the entire health plan. How do the clinical outcomes and costs associated with use of the new product compare with

existing alternatives? What are the implications for individual patients and for the entire Regence system?

Second, the new procedure will streamline the data acquisition and review process for Regence 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 the information expected by Regence. In addition, the standardized format allows Regence clinical staff to formally evaluate the completeness of submissions received and to easily add the results of their own literature reviews and analysis.

Initial experience with the process has been very encouraging. Orientation programs reviewing the submission guidelines were held in fall 1997 and were attended by representatives of nearly all the major pharmaceutical manufacturers. Most companies understood why submission of the dossier and outcomes modeling are important.

As of September 1998, 11 submissions have been received with preliminary modeling completed. (Two other submissions without modeling were returned to the submitting manufacturers and were not considered by the Regence P&T committee.) In 3 cases, the modeling was not well developed; the drugs were approved only on an interim basis to allow more time to complete the economic impact evaluation.

Up to this point, additional staff have not been necessary to support the process. The increased effort required by Regence clinical staff to evaluate submissions has been partially offset by the decreased time needed to gather data and prepare reports.

We recognize that many manufacturers may be reluctant to commit the necessary additional resources to complete these dossiers. If manufacturers view the process as a burden, rather than an opportunity, some submissions may be delayed or omitted entirely. Regence acknowledges this potential problem, but to date the process has not limited the ability of Regence's providers or patients to obtain appropriate drug therapy. We recognize that 3 factors have contributed to manufacturers' support: 1) Regence BlueShield is Washington's largest health plan and spends more than \$150 million annually on retail prescription drugs; 2) 45% of the Regence pharmacy health plans use a closed formulary; and 3) the major pharmaceutical manufacturers are already submitting outcomes modeling data

as part of submissions to national formularies in Australia, Canada and other countries. In an era of escalating healthcare costs, some manufacturers have realized that it was just a matter of time before major health plans in the United States would require this type of data.

The formalized system that Regence has developed to manage its formulary should be seen as a dynamic process. Flexibility on the part of Regence and manufacturers alike will be needed in the early stages. It is hoped that pharmaceutical manufacturers will commit increased resources to ensure that economic evaluations and modeling are available at the time of product launch. Regence will continue to evaluate its process and make adjustments when necessary to ensure that it continues to support the optimal care of Regence patients. Feedback from health plan providers, enrollees, and suppliers will play an important role in this ongoing process. After receiving a sufficient number of submissions, we intend to evaluate and publish a report detailing our experience with the process and any changes that have been required.

... CONCLUSION ...

Regence now requires manufacturers to complete a submission package addressing the clinical outcomes and economic consequences of using a proposed product. Because Regence clinical staff can easily combine information obtained from the submission dossier with the results of their independent literature reviews, the data acquisition and assessment process has been streamlined. More importantly, the process has improved the quality and relevance of the evidence available for formulary decisions.

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