The U.S. Food and Drug Administration: Drug Information Resource for Formulary Recommendations

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ABSTRACT

BACKGROUND: The U.S. Food and Drug Administration (FDA) is the regulatory agency responsible for approving all pharmaceutical products marketed in the United States. While the FDA does not conduct research for developing pharmaceutical products, the agency does review all of the scientific evidence that a pharmaceutical sponsor submits and ensures that it demonstrates U.S. regulatory standards for the product and meets approval requirements.

OBJECTIVES: To provide insights, for the managed care pharmacist, into the agency’s decision-making process and into the recommendations for appropriate usage and regulatory recommendations for risk mitigation by pharmaceutical sponsors.

METHODS: The FDA website contains a vast amount of clinically useful and meaningful information. This review focused on specific topics within the website that can be useful for the managed care pharmacist, including the following: (a) the FDA’s review and evaluation of new drug applications (NDA), supplemental new drug applications (s-NDA), and biological new drug applications (BLA); (b) materials regarding a therapeutic product presented to a public FDA advisory committee meeting; and (c) the postmarket requirements and commitments database that provides information on the studies that a sponsor must conduct to maintain a product’s approval for marketing in the United States.

RESULTS: This review examined the drug information contained on the FDA’s website and summarized the FDA’s medical and technical review, analysis and decision processes. Detailed drug information provided to the FDA by the pharmaceutical sponsor demonstrating a product’s efficacy and safety is publicly available upon the product’s approval.

CONCLUSION: For the managed care pharmacist involved with formulary review and recommendations, the FDA’s website contains information that is available to provide insight into the agency’s evaluation process and decision making for marketed pharmaceutical products. Use of these materials and understanding the regulatory context under which medical products are reviewed and approved may assist managed care pharmacists in making informed recommendations for use of the products within the context of their health systems.

J Manag Care Pharm. 2012;18(9):713-18

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The U.S. Food and Drug Administration (FDA) is the regulatory agency responsible for approving all pharmaceutical products marketed in the United States. While the FDA does not conduct research for developing pharmaceutical products, the agency does review all of the scientific evidence that a pharmaceutical sponsor submits and ensures that it demonstrates U.S. regulatory standards for the product and meets approval requirements. Throughout the drug development phases, the FDA has a long course of regular interaction with a pharmaceutical sponsor on its approach for meeting approval standards. The FDA’s review and evaluation of scientific evidence and the decisions reached once a product is approved are available to the public through the FDA’s website at www.fda.gov/cder. For the managed care pharmacist, the FDA’s reviews and evaluations provide insights into the agency’s decision-making process and into the recommendations for appropriate usage and regulatory recommendations for risk mitigation by pharmaceutical sponsors.

The FDA website contains a vast amount of clinically useful and meaningful information. This review focused on specific topics within the website, including the following: (a) the FDA’s review and evaluation of new drug applications (NDA), supplemental new drug applications (s-NDA), and biological new drug applications (BLA); (b) materials regarding a therapeutic product presented to a public FDA advisory committee meeting; and (c) the postmarket requirements and commitments database that provides information on the studies a sponsor must conduct to maintain the product’s approval for marketing in the United States.

Review and Evaluation of Therapeutic Products

The scientific evidence establishing a drug product as safe and effective is developed in a progressive stepwise fashion. Each step of scientific evidence informs the FDA about the product’s potential for meeting the rigorous scientific threshold to gain regulatory approval.

Before a potential therapeutic product may be studied in humans, it has to go through testing in the laboratory and in animals. Results from these nonclinical laboratory studies inform scientists about the best doses to use in order to begin testing in humans. These early tests also provide data on the manufacturing processes to produce the drug substance and, subsequently, the final drug product.
The FDA requires pharmaceutical manufacturers or “sponsors” to submit and assess these early laboratory data before studies in humans may proceed. While the FDA does not technically approve a study to begin in humans, the agency does review all the nonclinical scientific evidence and the proposed use of the potential drug product as planned in the clinical trial protocol. Based upon its review, the FDA can permit the study to proceed or choose to “hold” the study from beginning and ask the sponsor to correct any deficiencies. The investigation can resume only after the FDA notifies the sponsor that it may continue.

Throughout a product’s development, each new planned human clinical trial is submitted to the FDA before it may proceed. Cumulatively, the scientific evidence from studies in healthy subjects and patients, progressively developed study by study, can be classified according to the study’s objective and type as described in Table 1.

Most of the studies conducted under the human pharmacology, therapeutic exploratory, and therapeutic confirmatory category study classifications described in Table 1 establish efficacy and safety to support a marketing application. The FDA’s review and evaluation of these studies are available publicly on the FDA’s website.

### The FDA Reviewer’s Evaluation and Recommendations

Once a product or a new indication of a current product is approved, the FDA’s review, assessment, and decision actions taken are usually available to the public within 30 days through FDA’s website, www.fda.gov/cder. The web pages that contain the FDA’s reviews and evaluations of the scientific evidence submitted by pharmaceutical sponsors are located in a database called Drugs@FDA.

For long-awaited product approvals, managed care pharmacists may learn about the product approvals prior to the FDA’s complete posting of the materials on the website. A pharmaceutical manufacturer may have engaged with the professional community on pre-approval promotion, such as a “coming soon” advertisement.

Once the FDA has approved the product, the pharmaceutical manufacturer may begin to promote the product. However, in many cases, a product’s logistical distribution through the pharmacy warehouse and purchasing systems require preparation and coordination before the product is available for dispensing through standard pharmacy practices. The FDA’s usual 30-day time frame from a product’s approval to the time the scientific reviews are posted on the website often parallels the pharmaceutical manufacturer’s logistical time for preparing the product for distribution.

### Multidisciplinary Scientific Review

The searchable database Drugs@FDA, available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, contains official information for approved brand name and generic drugs and therapeutic biological products.

This database includes most drug products approved since 1939. The majority of labels and approval-related documents, including reviews, approval letters, and current and archived labels, are available for most drug products approved since 1998. This is an indispensable asset for managed care pharmacists who are responsible for drafting drug evaluation documents.

### Table 1: An Approach to Classifying Clinical Studies According to Objective and Type of Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Objective of Study</th>
<th>Study Examples</th>
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<tr>
<td>Human pharmacology</td>
<td>• Assess tolerance&lt;br&gt;• Define/describe pharmacokinetics (PK) and pharmacodynamics (PD)&lt;br&gt;• Explore drug metabolism and drug interactions&lt;br&gt;• Estimate activity</td>
<td>• Dose-tolerance studies&lt;br&gt;• Single and multiple dose PK and/or PD studies&lt;br&gt;• Drug interaction studies</td>
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<tr>
<td>Therapeutic exploratory</td>
<td>• Explore use for the targeted indication&lt;br&gt;• Estimate dosage for subsequent studies&lt;br&gt;• Provide basis for confirmatory study design, endpoints, methodologies</td>
<td>• Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures&lt;br&gt;• Dose-response exploration studies</td>
</tr>
<tr>
<td>Therapeutic confirmatory</td>
<td>• Demonstrate/confirm efficacy&lt;br&gt;• Establish safety profile&lt;br&gt;• Provide an adequate basis for assessing the benefit/risk relationship to support licensing&lt;br&gt;• Establish dose-response relationship</td>
<td>• Adequate and well-controlled studies to establish efficacy&lt;br&gt;• Randomized parallel dose-response studies&lt;br&gt;• Clinical safety studies&lt;br&gt;• Studies of mortality/morbidity outcomes&lt;br&gt;• Large simple trials&lt;br&gt;• Comparative studies</td>
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<tr>
<td>Therapeutic use</td>
<td>• Refine understanding of benefit/risk relationship in general or special populations and/or environments&lt;br&gt;• Identify less common adverse reactions&lt;br&gt;• Refine dosing recommendation</td>
<td>• Comparative effectiveness studies&lt;br&gt;• Studies of mortality/morbidity outcomes&lt;br&gt;• Studies of additional endpoints&lt;br&gt;• Large simple trials&lt;br&gt;• Pharmacoeconomic studies</td>
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Source: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.1
Drugs@FDA offers substantial information not available through other drug information resources. Searching for a therapeutic product, either by brand name or active ingredient, results in an overview of the product’s regulatory status. The dates of the FDA’s approval action, the NDA number, the chemical type, and the review classification for the drug product are listed. The chemical type and review classification may be useful information for determining whether the FDA deemed the drug’s or biologic’s developmental time frame.

Designations Assigned During the Drug Development Process

The orphan and fast track designations are granted by the FDA upon a sponsor’s request and demonstration that a product meets the criteria for the designation. These designations are independent of one another and are most often assigned during a drug's or biologic’s developmental time frame.

Orphan Product Designation. An orphan designation is granted to pharmaceutical products intended to treat diseases and conditions in which the prevalence is less than 200,000 Americans. If granted, the product may receive additional marketing exclusivity, waived user fees, and eligibility for drug development grants. In 2011, 37% of the new drugs approved were granted an orphan designation.

While orphan designation does not alter the standard regulatory requirements, in many cases, the sample size studied is small. This regulatory mechanism offers incentives to encourage drug development for diseases and conditions that may not otherwise have resources for development and marketing. When reviewing a product for formulary inclusion with an orphan designation, the population who will benefit may be small.

Fast Track Designation. Fast track designation may be granted during the clinical development phase for products intended to treat a serious or life-threatening condition and an unmet medical need. The fast track designation may be granted once proof-of-concept studies have been demonstrated. The designation facilitates frequent and interactive communication between the pharmaceutical sponsor and the FDA. Therefore, the fast track designation is of greatest benefit before the initiation of adequate and well-controlled studies to establish efficacy.

Often, products given the fast track designation may be suitable for a “rolling submission.” In this instance, the pharmaceutical manufacturer submits the marketing application to the FDA once a section of the marketing application is completed rather than waiting for the entire application to be submitted at one time. The rolling submission practice allows for the FDA’s scientific reviews to be conducted as pharmaceutical manufacturers complete individual sections and submit it. For example, the pre-clinical data package for the marketing application may be completed months before the final clinical studies have concluded and may be ready for submission to the FDA. However, if given a fast track designation, it may be beneficial for the pharmaceutical manufacturer and the FDA to have completed the pre-clinical studies and its review, leaving only the clinical studies and chemistry sections outstanding. The intent is to speed the development and the FDA’s review for treating serious and life-threatening diseases that do not have alternative therapeutic treatment options, that is, an unmet medical need.

Examples of serious diseases include AIDS, Alzheimer’s disease, heart failure, and cancer. However, diseases such as epilepsy, depression, and diabetes are also considered to be in this category. For each of these diseases, there are medical scenarios for which there are no other alternative treatment options available, thus, representing an unmet medical need.

Designations Assigned During the Review and Approval Process

Priority review and accelerated approval determinations are assigned at the time the application is submitted to the FDA. Each determination (priority review and accelerated approval) is independent of the other; however, it is often the case that an accelerated approval product is also deemed to be a priority review product.

Priority Versus Standard Review. At the time that the NDA is submitted to the FDA to begin the review of the marketing application, a designation is assigned to the product as either priority or standard. A priority designation is given when the therapeutic product is deemed to treat a disease where no satisfactory alternative therapy exists or where it is a significant improvement compared with marketed products, including nondrug products or therapies.

For priority designations, the FDA agrees to review and offer its response on a product’s approval status within 6 months rather than the 10-month review process for products designated standard review. It is not uncommon that a product granted a fast track designation during the drug development process may also be granted priority review upon a marketing application’s arrival at the FDA. To managed care pharmacists, knowing that a product has a fast track designation and priority review indicates that the product will treat a serious and life-threatening disease for which there is no other alternative treatment. Therefore, when considering formulary recommendations, knowledge of the priority designation will underscore the potential value of a product to treat a disease or condition where
no other satisfactory alternative therapy exists or where the product may be a significant improvement over other marketed products.

**Accelerated Approval.** Accelerated approval regulations (versus designation) allow for the approval of drugs for serious or life-threatening diseases on the basis of a surrogate endpoint; that is, the surrogate is reasonably likely to predict clinical benefit. For oncology-related therapeutics in which accelerated approval has been actively used, surrogate endpoints such as progression-free survival or tumor shrinkage may be predictive of overall survival and therefore a clinical benefit. One requirement for drugs approved under the FDA’s accelerated approval program is that the sponsor must study the drug further after approval to verify the expected clinical benefit. If confirmatory clinical trials do not demonstrate clinical benefit, the FDA has the authority to remove the drug (or the accelerated approval indication) from the market. For example, in 2004, the FDA determined that Iressa (gefitinib) should be withdrawn, since it failed to show overall survival advantage in treating patients with lung cancer. In 2011, the FDA revoked approval of the breast cancer indication for Avastin (bevacizumab); however, the drug remained on the market, since it also had been approved for certain types of colon, lung, kidney, and brain cancer. For the managed care pharmacist, knowing whether a therapeutic product received its approval as an accelerated or full approval is useful to understand whether confirmatory trials will be required. If the confirmatory clinical trials fail to demonstrate clinical benefit, the product or the accelerated approval product indication may be revoked by the FDA.

The FDA’s postmarket requirements and commitments database provides details on the clinical studies that must be conducted as a condition of approval, including the study’s objective, time frame, and reason for the requirement. Additional information on the searchable postmarket database may be found at: www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

### Drug and Biologic Therapeutics:

**Approval History, Reviews, and Related Documents**
As stated earlier, each new product or new indication (supplement) that is approved by the FDA has a corresponding entry within the database Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). Within each entry is a link to specific information about the product’s approval history, letter, reviews, and related documents. Table 2 provides an index of information to FDA source documents that includes the multidisciplinary scientific reviews. From the product name, additional hyperlinks are available to the comprehensive listing of each scientific discipline and administrative review as well as to the approval letter.

The medical review is one of the most useful documents for the managed care pharmacist to consider when preparing a therapeutic product recommendation for a health care system’s formulary. Information on the benefit-risk assessment, postmarketing recommendations, the application’s clinical trials, product chemistry, and pharmacology are integrated to provide an overall assessment of the product. Each review can comprise over 100 pages; therefore, it may be helpful to access the materials from the FDA website in order to determine which review and portions of reviews are most useful. Managed care pharmacists can use these materials to better understand the FDA’s decision making and consider these decisions when recommending the use of the medical product within their own health care systems.

For example, if the FDA approves a medical product that requires a risk evaluation and mitigation strategy (REMS) to be in place, there may be implications for prescribers and pharmacists when using this therapeutic product. The available FDA medical review provides a good understanding of the data evaluated, an understanding of what risks are expected to be mitigated through implementation of the REMS, and when and what will be evaluated by the FDA throughout the REMS implementation time frame. Knowing and understanding this, a managed care pharmacist may put forth recommendations that are made in the context of an ongoing regulatory requirement and postmarketing evaluation. Knowing that a REMS is intended to mitigate a particular risk along with prescribing and dispensing conditions, which may be required by the REMS, may impact the managed care pharmacist’s recommendation on how and when to consider use of the product within a health care system.

### Public Advisory Committee Materials
Prior to a product’s approval but upon completion of the pivotal clinical trials, the FDA may engage with independent external advisors on complex scientific, technical, and policy issues to obtain their professional expertise in the context of a
pharmaceutical product. FDA advisory committee meetings are often conducted so that the public can observe and, if they choose, voice their opinions about the questions asked by the FDA. Briefing materials, which provide relevant clinical data, are made available to committee members prior to the meeting. After each meeting, the briefing materials, webinars, and transcripts, along with the committee’s opinion via votes become available. These are other sources of product information that may be useful for managed care pharmacists to consider and evaluate when determining a therapeutic product’s characteristics and its potential value within their health care systems.

Not every pharmaceutical product will be taken before one of the FDA’s advisory committees. However, new molecular entity (NME) products or products that have a potentially challenging benefit-risk profile may go before an advisory committee. For specific products, advisory committees consider the available evidence and provide scientific and medical advice on safety, effectiveness, and appropriate use. Committees might also advise the agency on broader regulatory and scientific issues. The FDA generally follows an advisory committee’s recommendations, although it is not bound to do so.

Advisory committee materials for discussion and evaluation are available on the FDA’s website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm. These materials include the briefing book of data, slides, agenda, meeting roster, and minutes. The minutes include the questions and voting tally of the committee members as well as the public discussion details. These documents provide significant information for formulary evaluation, including the perspectives of the FDA, the manufacturer, the public, and the expert committee members.

### Postmarketing Requirements

#### Risk Evaluation and Mitigation Strategy (REMS)

An integral component of managing a formulary system includes making sure methods for ensuring safe prescribing, distribution, administration, and monitoring of medications are in place. The Food and Drug Administration Amendments Act (FDAAA) of 2007 gave the FDA the authority to require a REMS for manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. A REMS can be required for an individual drug or for a class of drugs whose components share a common set of risks. Some more restrictive REMS include elements to assure safe use (ETASU). These programs can require such tools as prescriber training or certification, pharmacy training or certification, dispensing to be restricted to certain health care settings, documentation of safe use conditions, required patient monitoring, or patient registries. These additional requirements are some considerations to be discussed at pharmacy and therapeutics committee meetings.

Resources are available to health care professionals to assist them in knowing when a new drug has a REMS and when a REMS has been created for a drug that already is on the market. The FDA website contains an up-to-date list of all drugs that have a REMS. The list includes the drug name, what elements comprise the REMS, and the date the REMS was approved. This list can be found by searching “Approved Risk Evaluation and Mitigation Strategies” at www.fda.gov.

The table on the FDA’s REMS website provides separate lists for the following:

- Currently approved individual REMS
- Currently approved single shared system REMS
- Released REMS

#### Postmarketing Study Commitments

After the FDA approves a product, the pharmaceutical manufacturer may conduct postmarketing studies. Understanding the postmarketing study commitments for a therapeutic product and the time frame in which the studies are to be conducted and completed can be useful when evaluating or re-evaluating formulary decisions. More information may be found on the FDA’s website at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PostmarketingPhaseIVCommitments/default.htm.

The FDA relies on the results of postmarketing studies to gather additional information about a product’s safety, efficacy, or optimal use. Agreements with sponsors to conduct postmarketing studies can be determined either before or after the FDA has granted approval for a sponsor to market a product.

To view the required postmarketing commitments for products approved by the FDA, there is an accessible database that is searchable from the FDA’s website located at: http://www.accessdata.fda.gov/scripts/cder/PMC/index.cfm. The information on the website, including additions and status changes, is updated quarterly. Certain information regarding postmarketing studies and clinical trials also may be obtained from ClinicalTrials.gov (www.clinicaltrials.gov).

### Conclusion

The FDA is responsible for the review, evaluation, and approval of all pharmaceutical products marketed in the United States. For the managed care pharmacist involved with formulary review and recommendations, the FDA’s website contains information that is available to provide insight into the agency’s evaluation process and decision making for marketed pharmaceutical products. Use of these materials and understanding of the regulatory context under which a product is reviewed and approved may assist managed care pharmacists in making informed recommendations for use of the medical product within the context of their health care systems.
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DISCLOSURES

The authors reported no funding for this manuscript and no financial or other potential conflicts of interest related to the subject matter of this manuscript.

All authors are employed by the U.S. Food and Drug Administration. The manuscript was primarily written by Marchand, with assistance from Rose and Fine; its revision, data collection, and data interpretation was primarily the work of Marchand with input from Rose and Fine. Kremzner assisted with data interpretation.

REFERENCES