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**THE STUDENTS' GUIDE TO ASSESS THE THERAPEUTIC VALUE OF A
NEW DRUG USING PROFESSIONAL PRODUCT LABELS**

DO NOT SUBSTITUTE LEXICOMP OR OTHER COMMERCIAL THIRD PARTY DRUG INFORMATION SOURCES FOR FDA APPROVED PROFESSIONAL PRODUCT LABELS.

When new drugs are approved by the Food and Drug Administration (FDA) what is the best independent source of information about the comparative therapeutic value, both safety and efficacy, of these new products? In the highly competitive markets for pharmaceuticals this question has become increasingly more difficult to answer.

At the time of FDA approval much of the information that is available to the public, including health professionals, about new drugs has been molded by manufacturers during the peer review process and in the lay media to create a positive therapeutic image of their new products. It is estimated that a sizeable portion of medical journal articles are “ghost managed” and “ghost written”, allowing the pharmaceutical industry to tactically place new products in front of health professionals and the public, in the best possible light, at the most strategic times for economic benefit.^{1,2}

Recent research suggests that about one-third of the clinical trials submitted to the FDA in support of the marketing approvals for the newer antidepressants were never published in the peer reviewed medical literature.³ Between 1998 and 2000 the FDA approved 90 New Molecular Entities (NMEs). An NME is a molecule that has never before been marketed in the U.S. Fewer than 50 percent of these trials submitted to support the approval of these 90 NMEs were not published five years post approval.⁴

The result of this type of selective publication is that the information readily available in the scientific literature to health professionals may be incomplete and potentially biased.⁵ These unpublished studies have been publically available free of charge on the FDA's Web site as new drug Briefing Documents and Approval Packages for a decade.⁶ Unfortunately, few authors have included these rigorously reviewed clinical trials in their publications resulting in avoidable publication bias.

The integrity of long-standing highly regarded drug information sources used by pharmacists including the American Hospital Formulary Service – Drug Information

(AHFS-DI) owned by the American Society of Health-system Pharmacists (ASHP); MICROMEDEX that includes DRUGDEX; and Clinical Pharmacology have come into question for the off-label prescribing of cancer therapies.^{7, 8}

These compendia's stated review methodologies varied considerably from their publishers actual practices. The compendia cited only a limited portion of the available evidence, often neither the most recent nor that of highest methodological quality. Of the 14 off-label cancer drug uses evaluated, the compendia differed in the indications included and whether and how they recommended particular agents for particular types of cancer. Revision schedules varied, and documentation practices made it difficult to determine whether and when content was updated.

The authors concluded that "current compendia lack transparency and do not seem to follow systematic methods to review or update evidence. Only off-label indications for cancer drugs were included in the study, and results cannot, correctly, be generalized to noncancer drug off-label or approved indications. Nevertheless, concern must remain with the independence and credibility of these reference resources.

Clinical practice guidelines have become the backbone for teaching therapeutics and drug selection to pharmacy students. Students with questions may be chastised by their instructors to check the guidelines. But, which guidelines – there are thousands? All too frequent the topic in the medical literature and the media is the quality and independence from influence of clinical practice guidelines. Bundling low quality clinical trials and attaching the worn term "evidence based" seems to confer magical credibility to guideline recommendations for clinicians.

The rigor of the evidence used to support the American College of Cardiology/American Heart Association (ACC/AHA) clinical practice guidelines have been critically evaluated over time. The number of recommendations has progressively increased, but these recommendations for the most part reflect a lower level of certainty.⁹

The print and broadcast media are not immune from conflicts of interest. In an essay in the *British Medical Journal* the authors warned that pharmaceutical manufacturers may be influencing reporters by creating endowed university chairs in academic journalism programs. Journalism awards are also offered and by the pharmaceutical industry.¹⁰ The prominent psychiatrist host of a the popular National Public Radio program "The Infinite Mind" was paid approximately \$1.3 million between 2000 and 2007 for giving promotional lectures for pharmaceutical manufactures. This income was not disclosed on the radio program. The weekly radio programs often touched on topics important to the economic interests of the companies for which the radio host consults.¹¹

All of this raises important questions about interpreting the medical literature and deciding and recommending which are the safest or most effective drugs. The first question is it now possible to conduct truly independent evaluations of the therapeutic value of new drugs when over one-half of the data may be unpublished? If 50 percent of the rigorously reviewed clinical trials submitted to the FDA are not published, then it is debatable that drug treatment recommendations based on the published literature are valid. On top of this are media with potential conflicts of interest that have a role in forming the images of the therapeutic value of new pharmaceuticals.

Second, what guidance should be given to students and consumers about deciding on the therapeutic value of new drugs? There are several possibilities. First, do not attempt an independent evaluation of new drugs until the FDA Approval Packages for the drug are posted on the Internet. The approval packages are the source of the unpublished trials used in the two studies cited above.^{3, 4} However, it may take as long as 60 days before these documents are available on the Internet. Also, you may not want to recommend a new drug until seven years after it has been approved unless there is clear evidence that the new drug offers some documented therapeutic advantage over older agents already on the market.¹⁰

In the current environment, a new drug's professional product label or package insert may be the most complete, rigorously reviewed, and objective source of information at the time of new drug approval. It is necessary to have familiarity with the FDA's standards for new drug approvals and the types of information that are contained in professional labels to effectively use professional labels to make comparative safety and efficacy decisions and recommendations.

The following recommendation for using professional product labels to assess the therapeutic value of new drugs is the result of conversations between faculty members at the School of Pharmacy – LECOM in response to the realization that because of the large number of clinical trials that are not published and other problems with the reporting of the therapeutic value of new drugs we can no longer simply tell our students to use the standard sources of new drug information that we have been recommending for years.

The Students Guide to Assessing the Therapeutic Value of New Drugs are a series of questions that are suggested to be asked and answered using professional product labels before forming an opinion on the therapeutic value of new drugs.

I. Assessing Efficacy: The Indications and Clinical Trials Sections of the Professional Product Label

A. New Drug Approvals Based on Placebo Controlled Trials

The best evidence for the benefit or the efficacy of a new drug is that drug's FDA approved use or uses. Placebo controlled trials provide the clearest evidence from a regulatory standpoint that drugs will do what their manufacturers say they will do which is the FDA's primary legislative charge from Congress in regulating drugs.

Note, there is nothing in the new drug approval standards that requires a new drug be either safer or more efficacious than products that are already available on the market.

A first step in forming an opinion about the therapeutic value of a new drug is to determine what outcome, or result, was used by the FDA to determine the drug's efficacy. This information is found in the Clinical Trials Section of the professional product label. Ask the question; is this outcome important to patients? For example, a drug that is approved on the basis of substantial evidence that it reduces the rate of fatal coronary events compared to standard therapy is an important outcome for both patients and their families.

In contrast, a new drug approved to treat overactive bladder that reduces, on average, the number of micturitions (urinations) by less than one per 24 hours from baseline compared to placebo may be of little or no importance to patients.

B. New Drug Approvals Based on Surrogate Endpoints

A manufacturer, in consultation with the FDA, may be allowed to define a disease based on a surrogate endpoint or marker because the actual cause of the disease is unknown and only manifestations of the disorder can be directly measured. Examples are rating scales for neurological disorders such as psychosis, depression, and Alzheimer's disease. Other examples of surrogate markers are tumor shrinkage, hemoglobin A_{1c} level, serum cholesterol concentration, and gastrointestinal lesions visible on endoscopy. Surrogate endpoints must be validated to ensure that an effect on the surrogate, in fact, translates to a clinically meaningful outcome. FDA approval based on surrogates communicates powerful images, perhaps overly optimistic, of benefit to the public and health professionals alike.

Whether or not the surrogate is a valid indicator of a clinically important outcome may be unknown. Efficacy is then defined by the agency and the manufacturer as the drug having a statistically positive effect on the surrogate marker in usually two randomized clinical trials.

The advisability of using surrogate endpoints to approve new drugs has been a long standing debate and has once again come under criticism spurred by the emerging safety issues surrounding rosiglitazone (Avandia) approved to manage type-2 diabetes.¹¹⁻¹³

The standard for approving new drugs to treat type-2 diabetes such as rosiglitazone has for years been positive effects on blood glucose and hemoglobin A1_c levels in pre-approval clinical trials. Both of these measures are surrogate endpoints. But, after decades of prescribing these drugs there is no evidence of a therapeutic benefit in reducing the macrovascular complications associated with type-2 diabetes.¹⁴ The FDA now requires the following statement in the professional product labels for all drugs approved to treat type-2 diabetes: “There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with [drug name] or any other anti-diabetic drug.”

C. Approvals Involving Active Comparators

Ethical considerations prevent the use of placebo controls in clinical trials for some conditions, for example, acute pain, active infections or diabetes. The main question to ask here is if the comparison is fair?

Examine if the best available drug treatment is being used as the comparator and if it is being used at the most effective dose and dosing frequency.

D. Approvals of Antibiotics

New antibiotic approvals represent a special case that has come under scrutiny because of the FDA allowing the use of a type of trial design known as non-inferiority trials to support new antibiotic approvals. For ethical reasons subjects with active infections cannot be randomized to receive a placebo control. In trials of new antibiotics the comparator should be the best available therapy, either monotherapy or combined drug treatment. A non-inferiority trial provides evidence that the new antibiotic is no worse than what is already available on the market.

The approval of telithromycin (Ketek), a first in class ketolid antibiotic, drew the attention of Congress because, in part, its approval was based on non-inferiority trials. Safety changes were ultimately made to telithromycin’s professional product labeling.^{15, 16}

The approval standard using non-inferiority trials for new antibiotics may in some cases be viewed as a demonstration that the new antibiotic is no worse than products currently on the market in terms of efficacy. However, as was the case with telithromycin safety is not addressed in non-inferiority trials.

Non-inferiority trials can be difficult to interpret. The FDA convened a meeting of its Anti-Infective Drugs Advisory Committee Meeting in November 2008 to review the Justification of Non-Inferiority Margin for the Treatment of Complicated Skin and Skin Structure Infections.¹⁷

E. What Was the Size of the Difference Between the New Drug and the Comparator?

The clinical trials described in the Clinical Trials section of the professional label will allow for a comparison of the size of the effect of the new drug versus a placebo or active control. The important question to ask is if this difference is important to patients. The determination of importance may differ between health professionals and consumers.

For example, the difference between the drug fesoterodine (Toviaz), a drug approved to treat overactive bladder, and placebo is the mean change from baseline for the number of micturitions (urinations) after 12 weeks of treatment ranged from 0.72 to 0.92. This decision must be made if this difference is important. If it is, then it is clinically significant.

Professional product labels can also be used to make comparison between the effects of two drugs that are approved using the same efficacy outcome variable as allowed by the FDA. Again, using fesoterodine as an example, tolterodine (Detrol) is a logical comparator as fesoterodine was developed from the main active metabolite of tolterodine.

Comparing the results reported in the Clinical Trials sections of fesoterodine with tolterodine the result is a difference of 0.42 micturitions in the mean change from baseline per 24 hours. Ask if this difference is important.

There are pitfalls in trying to compare different drugs using professional product labels. The primary problem is that the study populations for the two drugs are different limiting the ability to make valid comparisons.

II. Are Superiority Claims for the New Drug Made in the Professional Product Label?

A key question for health professionals and consumers is which drug is the best drug? The answer to this question is largely unknown at the time a new drug is approved because there is no legal standard that requires that new drugs be therapeutically superior to already available products.

Legally, a claim of superiority for either safety or efficacy can only be made and promoted by a manufacturer if a statement of superiority appears in a drug's FDA approved professional product label. This would require the successful completion of comparative (head-to-head) trial showing superiority. The results must then be reviewed and approved by the FDA before the claim can be added to the drug's professional product label.

If a claim of superiority does not appear in the drug's professional product label, assume that no valid data exists to support such a claim. And remember, that it may no longer be possible to assess independently the comparative therapeutic value of new drugs by relying on the peer reviewed medical literature.

III. Assessing Safety

Relatively little is known about the safety of new drugs compared to their efficacy. This is largely due to the small sample size and limited duration of pre-approval clinical trials. There is no acceptable surrogate for drug safety and infrequent but serious adverse drug reactions may not be detected until the product is in general use.

A new drug in a crowded pharmacological class with older widely used agents may present unique risks that are unacceptable. Cerivastatin (Baycol) was the sixth statin drug approved in the U.S. to lower cholesterol. The drug was removed from the market in August 2001 because of reports of rhabdomyolysis. A similar pharmacological action does not necessarily ensure similar safety.

The nonsteroidal anti-inflammatory drugs (NSAIDs) rofecoxib (Vioxx) and valdecoxib (Bextra) were among the over 20 NSAIDs available on the U.S. market at one time. These drugs were withdrawn from the market in September 2004 and April 2005 respectively for safety reasons. These two NSAIDs were ultimately found to be less safe than existing agents and no more effective.

Because new drugs are not required to be more effective than older agents approved for the same uses and their safety is largely a question mark. The prudent course may be not to recommend the use of a drug until seven years after it has been approved.

IV. Accessing Professional Product Labels

There are two free sources of FDA approved professional product labels available on the Internet:

1. DailyMed (<http://dailymed.nlm.nih.gov/dailymed/about.cfm>)

This Internet site is a cooperative initiative between the National Library of Medicine and the FDA. Eventually all professional product labels for drugs marketed in the U.S. will be available to the public free of charge.

The goal is to have these labels updated in real time.

DailyMed is user friendly and has a medical dictionary option that links technical terms to a medical dictionary for their definitions.

2. Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>)

This is a very valuable resource to search for official information about FDA approved brand name and generic drugs and therapeutic biological products.

The main uses of Drugs@FDA are:

- finding professional product labels for approved drug products
- finding generic drug products for a brand name drug product
- finding therapeutically equivalent drug products for a brand name or generic drug product
- finding consumer information for drugs approved from 1998 on
- finding all drugs with a specific active ingredient
- viewing the approval history of a drug

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