

FDA's Drug Approval Process: Up to the Challenge?

Bill Number:

Hearing Date: March 1, 2005, 9:30 am

Location: SD106

Witness:

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Testimony

Thank you for the invitation “to provide my professional opinion on what, if anything, Congress and the FDA need to do both to protect and to promote the public health with respect to drugs and biologics, including a discussion about what changes might need to be made to ensure that FDA is fully considering both benefits and risks during pre- and post-market review”. My testimony is based on 28 years experience in collaborating on the design, conduct and analysis of government and industry sponsored clinical trials, and on nearly 20 years service on FDA Advisory Committees.

Executive Summary

- A. Decisions regarding marketing of drugs and biologics should be based on robust and compelling evidence that the intervention has a favorable benefit-to-risk profile.
- B. In general, the FDA has been very effective in carrying out its regulatory responsibilities and, in turn, has had a profoundly favorable influence on the process of promoting and protecting public health.
- C. In evaluating effects of Cox-2 inhibitors on the risk of cardiovascular mortality, MI and stroke, the FDA proceeded in a proper manner regarding the accumulation of data from observational studies and randomized trials and regarding the development of benefit-to-risk assessments for this class of agents using these data.
- D. The FDA should retain the responsibility for evaluation of safety of drugs and biologics.
- E. Multiple sources of information are useful in monitoring for safety signals, including i) pre-marketing evaluations (usually from randomized controlled trials) that are of sufficient size and duration to provide robust and compelling evidence that the product has a favorable benefit to risk profile; ii) post-marketing passive surveillance, such as is provided by the Adverse Event Reporting System (AERS); iii) post-marketing active surveillance, such as is provided by large linked data bases, in particular for products that will have wide spread use; and iv) post-marketing randomized trials to rule out unacceptable increases in the rate of clinically significant safety risks that are uncommon or occur on a delayed basis, when evidence has been obtained to suggest the plausibility of such risks.

F. Some modifications that would need to be effected by legislation would enhance the effectiveness of the FDA. These include: i) providing increased funding to FDA to support scientific pursuits and improve regulatory effectiveness of reviewers; ii) encouraging FDA reviewers to communicate more effectively with the public; iii) when safety risks are found, requiring controlled studies (usually randomized trials) that have the ability to determine whether an unacceptable safety risk truly exists be conducted in a timely manner; iv) improving methodology for safety monitoring in children; v) establishing a funding program at FDA for observational studies and clinical trials; and vi) for agents that have received Accelerated Approval under subpart H, ensuring the FDA has policies in place regarding timeliness of completion of validation trials and prompt withdrawal of the product from the market if the validation trials fail to provide robust and compelling evidence that the product has a favorable benefit-to-risk profile.

Introduction

The regulatory approval of drugs and biologics for marketing in new clinical indications should be based on evidence from adequate and well controlled clinical trials that reliably establish that the product has a favorable benefit-to-risk profile. Therefore, these clinical trials must give robust and compelling evidence that the product provides clinically and statistically significant beneficial effects on clinical efficacy outcomes that unequivocally reflect tangible benefit to patients. Examples of such beneficial effects would be relieving disease related symptoms, improving the ability to carry out normal activities, or reducing hospitalization time while, in the setting of life threatening diseases, the most important beneficial effect often would be prolonging survival. In turn, sufficient safety data should be obtained to provide reliable evidence that these beneficial effects outweigh the safety risks to patients who will use these products in a real world setting. It follows that the level of safety risks that would be judged to be “acceptable” would depend on the level of benefit provided by the intervention.

While sponsors from industry and sponsors from government agencies other than FDA regularly make valuable contributions to the development of greatly needed interventions for treatment and prevention of disease, the reality is that important financial and professional conflicts of interest can result in advocacy for marketing products that have not been established reliably to be safe and effective, placing the public at significant risk. In general, the FDA has been very effective in carrying out its responsibilities to regulate the activities of these sponsors, to ensure that products that are being marketed truly do have a favorable benefit-to-risk profile. Through this achievement, the Agency has had a profoundly favorable influence on the process of promoting and protecting public health.

Before discussing potential refinements to the FDA drug approval process, some aspects of the current process for evaluating safety and efficacy should be reviewed.

Evaluating Safety: Some Background Regarding Available Approaches

The review of safety of new products is a complex and multidimensional undertaking. The FDA considers reports of adverse drug reactions from available clinical data, pursues concerns raised by animal toxicology, pursues insights from pharmacokinetic and pharmacodynamic assessments including potential risks of drug-drug interactions, looks specifically for class effects, and searches for rare events. This effort is guided by their

wealth of experience. For example, before approval, lack of adverse effects on patient survival must be established for most new drugs for heart failure (due to the experience with inotropes) and for antiarrhythmics (due to the experience with encainide and flecainide).

There are several clinical data sources providing insights about safety risks of new products. In the pre-marketing setting, the most reliable of these sources is the randomized controlled trial. Pre-marketing clinical trials should be of sufficient size and duration to provide robust and compelling evidence that the product has a favorable benefit to risk profile. When evaluating products (such as analgesics, antihistamines, antidepressants, and asthma remedies) not expected to reduce mortality or to prevent irreversible morbidity (such as reducing the risk of stroke, permanent loss of vision, or HIV infection), one might need evidence from randomized trials that cumulatively involve more than 10,000 patients. This is particularly important when available evidence suggests plausibility of clinically significant safety risks. The evaluation of Cox-2 inhibitor pain relievers provides an illustration. Given that products in this class provide only a limited reduction in risk of significant upper GI ulcers and have not been established to provide improved pain relief relative to non-specific NSAIDs such as naproxen, new members of the Cox-2 inhibitor class should not be approved until evidence is available from randomized trials ruling out the possibility that these new agents induce a 50% relative increase in the risk of major cardiovascular (CV) events, including CV deaths, MIs and stroke, (i.e., ruling out that the drug causes at least 5 additional major CV events per 1000 patients treated, in a population having a background rate of such events of 1%).

Once the product is approved, it is important to continue monitoring for safety signals. Post-marketing passive surveillance, such as is provided by the Adverse Event Reporting System (AERS), is useful for detecting large increases in clinically important rare events, such as establishing the risk of intussusception with a rotavirus vaccine, or assessing the risk of encephalopathy with the acellular pertussis vaccines, or detecting the risk of Stevens-Johnson rash in the treatment of patients infected with HIV. The Office of Drug Safety is responsible for monitoring AERS. However, this system has significant limitations. It is based on voluntary submission of MedWatch forms for adverse events that caregivers believe might be drug related. Underreporting, the lack of denominators and the lack of comparator groups make such information very difficult to interpret in many settings. These types of irregularities in safety information have led to considerable difficulties in the assessment of the relationship of the class of Selective Serotonin Reuptake Inhibitor (SSRI) agents regarding the risk of suicidal ideation and/or attempts. Post-marketing active surveillance, such as is provided by large linked data bases (the Northern California Kaiser data base being a classic example), provides an improvement over passive surveillance, through more systematic collection of adverse events, yielding complete numerators (i.e., safety events) and denominators (i.e., people exposed to the product). This enhanced approach to post-marketing safety assessment should be more widely implemented for products that will have widespread use. This type of evidence could significantly enhance the insights into whether there is a true causal relationship between SSRI agents and the risk of suicidal ideation and/or attempts. However, this approach also has important limitations. Due to lack of a randomized control group, frequently unavailable confounder information (such as aspirin use or smoking history

when studying Cox-2 inhibitors), concerns regarding outcome specificity (are reported events truly events?) and sensitivity (are true events reliably captured?) partly due to recall bias, and concerns resulting from loss to follow-up and the lack of a proper “time 0” cohort, results from these analyses can be very misleading, especially when one is attempting to determine whether an intervention induces a clinically important safety risk that corresponds to less than a 2-fold increase in rate of occurrence of these safety events. These concerns appear to be relevant to the setting of Cox-2 inhibitors. While their effect on the risk of CV deaths, MI and stroke is clinically significant, it appears that this effect is approximately at the level of a 1.5 fold increase. In such settings, the FDA properly would view such “epidemiological” or “observational” evidence to be hypothesis generating or clues regarding safety signals. The FDA properly recognized that it was necessary to conduct post-marketing randomized trials, with large sample sizes and long term follow-up, to reliably address the CV safety risk of the Cox-2 inhibitor class. When an important safety signal has been suggested but has not clearly been established by active and passive surveillance, post-marketing randomized trials should be conducted to rule out unacceptable increases in the rate of clinically significant safety risks that are uncommon or occur on a delayed basis. The aggregation of evidence from such large scale randomized trials, conducted in pre- and post-marketing settings, has served as the most reliable source of information to address class effect of Cox-2 inhibitors regarding risk of CV death, MI and stroke. In order to have high reliability in detecting a tripling in the rate of a serious safety event that would occur at the rate of 1 per 1000 patients, the post-marketing randomized trial would need to have approximately 20,000 patients. Several examples exist, in addition to the Cox-2 setting, where trials of this type have been conducted. Two such examples are the evaluation of the cardiovascular mortality risks of anti-psychotics known to induce increases in QTc, and the assessment of the risk of respiratory-related deaths and respiratory-related life-threatening experiences in patients currently receiving prescription asthma medications. Large post-marketing clinical trials have frequently provide insights about safety risks that were inconsistent with prior expectations based on observational studies or effects on biomarkers (i.e., surrogate endpoints). For example, the ALLHAT trial established that a calcium channel blocker did not have adverse effects on cancer risk, MI or death, and the Women’s Health Initiative showed that observational studies improperly characterized the effects of hormone use in women on cardiovascular risk. In a stunning example, even though encainide and flecainide had been shown to suppress arrhythmias, a known risk factor for sudden death (resulting in off-label use annually by hundreds of thousands of Americans), the 2000 patient CAST trial established that these antiarrhythmic agents actually tripled the death rate. Even though the overall death rate was tripled by these agents, this excess risk was not recognized until the availability of the results of the randomized trial.

Evaluating Efficacy

As discussed earlier, drug safety cannot be considered separately from drug efficacy/effectiveness since they are both part of an overall assessment of benefit-to-risk. This was recognized in 1962 when the Food Drugs and Cosmetic Act was amended to include that drugs should demonstrate substantial evidence of efficacy as well as safety. A rich science exists regarding design, conduct and analysis issues that are influential in

the achievement of robust and compelling evidence that a product provides clinically and statistically significant beneficial effects. These issues therefore have major regulatory importance, and draw a great deal of attention from both clinical and statistical reviewers at the Agency. Some of these that frequently are most critical in the interpretation of efficacy data are: i) factors that influence bias and variability, including the role of randomization, the influence of loss to follow up, the need to conduct intention to treat analyses, and the role of blinding; ii) choosing proper endpoints, and the role of biomarkers as surrogate endpoints; iii) avoiding biocreep when conducting non-inferiority analyses to establish efficacy of new products when being compared to standard of care interventions; iv) the role of subgroup analyses; and v) procedures for monitoring registrational trials to address ethical and scientific concerns.

The second issue in the previous paragraph deserves particular attention. It is often proposed that regulatory assessments of efficacy be based on evaluation of effects on biomarkers, such as transient tumor shrinkage in oncology, or suppression of arrhythmia in cardiology, or decolonization for antimicrobials, rather than evaluating effects on clinical efficacy outcomes that unequivocally reflect tangible benefit to patients, such as duration of survival, disease-related symptoms, or ability to carry out normal activities. The use of biomarkers as replacement or “surrogate” endpoints for the clinical efficacy outcomes enables trials to be conducted with smaller numbers of patients and in shorter periods of time. Regrettably, these surrogate endpoint trials often give misleading results about whether the product truly provides beneficial efficacy, as illustrated earlier by the fact that encainide and flecanide suppress arrhythmias and yet have an adverse effect on mortality.

The Accelerated Approval (AA) (subpart H) regulatory process was established to allow marketing of products that have been shown to have compelling effects on biomarkers, if these effects are “reasonably likely to predict clinical benefit”, and if the sponsor completes, in a timely manner, one or more trials that will validate that the intervention truly does provide meaningful beneficial effects on true clinical efficacy outcomes.

Unfortunately, as discussed in the accompanying publication (Fleming TR, “Surrogate Endpoints and FDA’s Accelerated Approval Process: The challenges are greater than they seem”, *Health Affairs* 24: 67-78, 2005), many challenging issues arise from the implementation of the AA process that can lead to compromising what is truly in the best interest of public health: the reliable as well as timely evaluation of an intervention’s safety and efficacy. This publication discusses policies that Congress and the FDA should consider to reduce the likelihood that products are used for a lengthy interval of time by patients in non-research settings, even though efficacy has not been established and available safety data are much more limited than what would typically be available from completed trials evaluating effects on clinical efficacy outcomes.

Potential Refinements to the FDA Drug Approval Process

The FDA is not “broken”. The process of drug review works very well. In general, the FDA has been very effective in carrying out its regulatory responsibilities and, in turn, has had a profoundly favorable influence on the process of promoting and protecting public health. Leaders at FDA such as Robert Temple, M.D., (Director, Office of Medical Policy; Director, Office of Drug Evaluation I), are extremely knowledgeable, fair, and

highly effective in guiding the FDA in the achievement of its mission. Such people are national treasures.

Even though the FDA process for drug review is one of the best in the world, some modifications that would need to be effected by legislation would enable important improvements. Before discussing these, it should be noted that one change that should not be made is the creation of a separate group, outside FDA, to review safety or efficacy. First, the regulatory experts at FDA have particular experience and familiarity with the drug approval process including the Code of Federal Regulations and the limits of the authority of the FDA. Second, it is unclear how the recommendations of such an outside organization would be incorporated into the functioning of the FDA. Finally, there are significant conflicts of interest issues for many outside FDA who might be selected to serve in a separate safety group.

The following are potential changes regarding FDA that should be considered:

1. Increase funding to FDA to allow more person power to accomplish necessary tasks, while allowing reviewers time for scientific pursuits that will improve their regulatory effectiveness. Increased funding would also allow better research within FDA on clinical trials methodology.
2. FDA reviewers should have better communication with the public. Reviewers should be encouraged to publish important points or summaries of their reviews in peer reviewed publications in order to better inform the public regarding efficacy and safety of drugs. (Many scientific articles published by the academic and industry scientists have a “sponsor spin”, resulting in reduced objectivity and biased presentation of evidence regarding the benefit to risk profile of the product.)
3. When a safety signal is found, frequently from non-controlled post-marketing data, FDA should require that controlled studies (usually randomized trials) that have the ability to determine whether an unacceptable safety risk truly exists, be conducted. When such trials are conducted in post-marketing settings, requirements for timely completion should be in place.
4. Safety monitoring in children needs better methodology. Currently, the ability to assess rare or long term safety risks, such as for SSRIs, too often is inadequate. Furthermore, when it is unclear how to measure an adverse event in a child, the sponsor should be required to develop methodology to study the safety event in order to be allowed to pursue an indication if the disease is not serious or life threatening.
5. An FDA funding program for observational studies and clinical trials should be established. Among the uses for these funds would be i) enabling the FDA to have access to evidence from large linked data bases, allowing timely detections of safety signals once products are marketed, in particular for products that will be widely used in settings where rare or long term safety risks could lead to an unfavorable benefit-to-risk profile; ii) enabling the conduct of important placebo controlled efficacy and safety trials as well as those with generic drugs that will not be conducted by industry or NIH; and iii) providing funding to develop better tools for clinical trials in the Critical Path program headed by Dr. Janet Woodcock.

6. For interventions that are allowed to be marketed under (subpart H) accelerated approval, the FDA should have policies requiring that clinical trials are in place at the time of the accelerated approval that can reasonably be expected to provide statistically compelling evidence, within a well-defined rapid time frame, about whether the intervention as a favorable benefit-to-risk profile by being safe and by providing clinically meaningful tangible benefit to patients; and the product will be withdrawn from the market promptly if the validation trial does not conclusively provide this required positive evidence.