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**THE FOOD AND DRUG
ADMINISTRATION'S (FDA)
ACCELERATED APPROVAL
PROCESS AND THE FAILURE
TO VALIDATE SURROGATE
ENDPOINTS**

The Food and Drug Administration (FDA) has the option of using two different legal standards for approving new drugs. The most familiar of these is known as the standard approval process that is based on the criterion of substantial evidence, not absolute proof, of a drug's safety and efficacy. In Section 505 of the Food, Drug and Cosmetic Act substantial evidence is defined as:

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that

the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

The FDA can also approve drugs under an accelerated approval process created by the FDA to allow severely ill patients early access to promising new treatments. In December 1992, the FDA published new regulations (21 CFR 314, subpart H and 601 subpart E) to provide for this accelerated review process for drugs that treat serious and life-threatening illnesses and that provide meaningful therapeutic benefits over existing therapies. In 1997, Congress passed the FDA Modernization Act (FDAMA) which incorporated this approach into law in Section 112 of FDAMA (Section 506 of the act; 21 U.S.C. 356). Drugs or biologicals approved under the accelerated approval process are often referred to as subpart H or subpart E drugs.

Under the accelerated approval process, the FDA may approve drugs based on a surrogate endpoint, or biochemical marker, that is reasonably likely to predict a clinical benefit. However, the manufacturer, or sponsor, of the drug must conduct postmarketing

studies to validate a clinical benefit. The accelerated approval process allows the drug on the market sooner but with less evidence of clinical efficacy than is required under the standard approval process. The FDA can withdraw marketing approval if the required postmarketing studies are not completed with due diligence or if the studies fail to verify a clinical benefit of the drug. The statute governing this process is Section 506 of the Food and Drug Administration Modernization Act of 1997 (21 U.S.C. 356), which states:

The Secretary may withdraw approval of a fast track product using expedited procedures (as prescribed by the Secretary in regulations which shall include an opportunity for an informal hearing) if—

(A) the sponsor fails to conduct any required post-approval study of the fast track drug with due diligence;

(B) a post-approval study of the fast track product fails to verify clinical benefit of the product;

(C) other evidence demonstrates that the fast track product is not safe or effective under the conditions of use; or

(D) the sponsor disseminates false or misleading promotional materials with respect to the product.

Surrogate endpoints are laboratory measurements or physical signs used as substitutes for clinically meaningful endpoints that directly measure how a patient

functions or survives. Examples of surrogate endpoints are suppression of ventricular arrhythmias, reduction in cholesterol or blood pressure, and tumor regression in cancer treatment trials.¹

Unfortunately, it appears that compliance with the regulation to conduct post marketing studies to validate clinical benefit by manufacturers who have received marketing authorization for their drugs under the accelerated approval process is poor. This is according to a Staff Report by Representative Edward J. Markey of MA released on June 1, 2005.² The full text of this report can be found on the Internet at http://www.house.gov/markey/Issues/iss_health_rep050601.pdf.

The Markey Report found that since 1992, 28 companies have made 91 postmarketing study commitments for 42 different drugs approved under the accelerated approval process. As of March 9, 2005 the status of these study commitments is:

- 46% (42/91) of the study commitments that were made were not complete.
- 50% (21/42) of outstanding accelerated approval confirmatory studies have not been started, even though the drug is being marketed to consumers. Companies have been

selling these drugs to the public for an average of 1 year and 10 months and up to 6 years and 9 months without even initiating the required studies.

- 7% (3/42) of outstanding accelerated approval confirmatory studies have been initiated but are behind schedule.
- 43% (18/42) of outstanding accelerated approval confirmatory studies

are proceeding.

- There have not been any withdrawals of the products approved under accelerated approval related to a failure of the sponsor to conduct the required post-marketing confirmatory trial.

According to the Report there are currently 16 drugs that have outstanding confirmatory studies. These are listed in Table 1 below:

Brand name/ Generic Name	Manufacturer or Sponsor	Approval Date
Alimta/ pemetrexed	Eli Lilly	8/14/2004
Arimidex/ anastrozole	AstraZeneca	9/5/2002
Celebrex/celecoxib	GD Searle	12/23/1999
DepoCyt/ cytarabine	Skyepharma	4/1/1999
Ethylol/ amifostine	Medimmune	03/15/1996
Gleevec/ imatinib	Novartis	12/20/2002
Iressa/ gefitinib	AstraZeneca	5/5/2003
Luveris/ lutropin alfa	Serono	10/8/2004
Mylotarg/ gemtuzumab	Wyeth	5/17/2000
Proamatine/ midodrine	Shire	9/6/1996
Remodulin/ treprostinil	United Therapeutics	5/21/2002
Sulfamylon/ mafenide	Mylan	6/5/1998
Synercid/ dalfopristin; quinupristin	King	09/21/1999
Truvada/ emtricitabine; tenofovir	Gilead	8/2/2004
Velcade/ bortezomib	Milennium	5/13/2003
Viread/tenofovir	Gilead	10/26/2001

Current professional product labels provide information regarding the safety and effectiveness of an accelerated approval drug when the confirmatory studies are still incomplete. Yet, the labels appear to be just as complete as the information on fully approved drugs where all of the studies were

completed and the clinical benefit was confirmed prior to approval. This is misleading to patients and physicians alike. The FDA should at least inform the patient and medical communities of the fact that studies that are necessary to confirm the safety and effectiveness of

accelerated approval drugs are not complete.

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REVIEW OF RISPERIDONE (RISPERDAL CONSTA) FOR SCHIZOPHRENIA

Long-acting risperidone injection (Risperdal Consta) produced by Janssen Pharma was approved by the Food and Drug Administration (FDA) in October 2003 for the treatment of schizophrenia. The drug is an extended release form of risperidone, microencapsulated in biological polymers, to be administered every two weeks by IM injection.

The specific question addressed in this review is what evidence is available from randomized controlled trials (RCTs) that long acting risperidone injection is therapeutically superior, with regard to either safety or efficacy, compared to other FDA approved injectable drugs for schizophrenia. At this time, the FDA has not approved any statement in the professional product labeling for long-acting injectable risperidone stating that it is therapeutically superior to other marketed long-acting antipsychotic agents.¹

The National Library of Medicine's PubMed database was searched using "Schizophrenia/drug therapy" AND "Risperidone" AND "Delayed-Action Preparations" as search terms. The search results were limited to RCTs, English language, and Human studies.

Studies and articles published in medical journal supplements, throwaway journals, and published abstracts are excluded from this review. Evidence suggests that RCTs published in journal supplements are generally of inferior quality compared with articles published in the parent journal.² Throwaway journals are characterized as those that contain no original investigations, are provided free of charge, have a high advertisement-to-text ratio, and are non-professional society publications. They have been found to be lower in methodologic and reporting quality than journals containing original investigations.³ Published abstracts are also excluded from this review as only approximately one half of all studies initially presented in abstract form may subsequently be published as full-length reports.⁴

A total of four studies were identified using the above criteria.⁵⁻⁸ Three of these studies were excluded from this evaluation. One of these three studies, Nasrallah et al., examined the health related quality of life of patients treated with long-acting risperidone.⁶ Chue and colleagues evaluated the safety and efficacy of long-acting risperidone compared to risperidone oral

tablets.⁸ The third study excluded was Lauriello et al.⁷ that evaluated a subgroup of inpatients originally evaluated in the Kane et al.⁵ study.

Also included in this review is the FDA’s evaluation of data submitted by Janssen Pharma in support of long-acting risperidone injection’s approval. This information is available on the agency’s Web site at

www.fda.gov/cder/foi/nda/2003/21346_RisperdalTOC.htm. The inclusion of these analyses by FDA scientific staff has become mandatory as it is no longer possible to conduct an independent evaluation of the therapeutic value of a new drug by relying solely on the published medical literature.

The FDA accepted the safety and efficacy of long-acting risperidone based largely on data reviewed for the approval of the oral

dosage form of the drug. The New Drug Application submitted to the FDA for long-acting risperidone consisted of three phase III studies. The agency choose to review only one of these, Kane et al.⁵, that compared long-acting risperidone in doses of 25 mg, 50 mg, and 75 mg to placebo over 12 weeks using the Positive and Negative Syndrome Scale (PANSS) as the primary efficacy endpoint.⁹

There were 400 patients with schizophrenia enrolled in the double blind phase of the Kane et al. trial. Of these 400 patients, only 176 completed the study giving a drop out rate of 56 percent during the 12 week duration of the trial. Most discontinuations were for insufficient response and adverse events.

Table 1 below summarizes by treatment group the reasons that patients discontinued the trial.

Table 1 – Reasons for Discontinuation of Trial Medication for Patients with Schizophrenia				
Trial Termination Reason	Placebo N = 98	Risperidone 25 mg N = 99	Risperidone 50 mg N = 103	Risperidone 75 mg N = 100
Termination for any reason	67 (68.4%)	51 (51.5%)	53 (51.5%)	52 (52.0%)
Insufficient response	29 (29.6%)	22 (22.2%)	15 (14.6%)	12 (12%)
Adverse event	12 (12.2%)	11 (11.1%)	12 (11.7)	14 (14.0%)
Death	1 (1.0%)	0	0	0
Other	5 (5.1%)	6 (6.1%)	4 (3.9%)	4 (4.0%)
Ineligible to continue trial	0	3 (3.0%)	3 (2.9%)	3 (3.0%)
Lost to follow-up	6 (6.1%)	2 (2.0%)	3 (2.9%)	6 (6.0%)
Non-compliant	4 (4.1%)	0	3 (2.9%)	3 (3.0%)
Withdrew consent	10 (10.2%)	7 (7.1%)	13 (12.6%)	11 (11.0%)

As mentioned above the primary efficacy variable was the change from baseline in total PANSS score at endpoint. The results of the Last

Observation Carried Forward (LOCF) analysis for patients with schizophrenia are summarized in Table 2 below.

Table 2 – Total PANSS Score – Mean and Mean Change from Baseline to Endpoint – LOCF Analysis for Patients with Schizophrenia								
	Placebo		Risperidone 25 mg		Risperidone 50 mg		Risperidone 75 mg	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	92	82.0 (1.54)	93	81.7 (1.32)	98	82.3 (1.41)	87	80.1 (1.53)
Endpoint	92	84.5 (2.12)	93	75.6 (2.35)	98	73.6 (2.03)	87	74.5 (2.31)
Mean change from baseline	92	2.5 (1.73)	93	-6.1 (2.08)	98	-8.7 (1.55)	87	-5.6 (1.88)
P-value			0.002		<0.001		<0.001	

The mean change in PANSS from baseline was numerically the best in the long-acting risperidone 50 mg group with an average improvement of 8.7 points.

A major safety concern with long-acting risperidone and other atypical antipsychotics is increased mortality in elderly patients with dementia related psychosis. An analysis of 17 placebo controlled trials in these patients found a risk of death of between 1.6 and 1.7 times that seen in placebo treated patients.

Over the course of a typical 10 week trial, the death rate in drug treated patients was about 4.5 percent compared to 2.6 percent in patients receiving placebo.¹ This equates to a Number Needed to Harm of 53 patients for 10 weeks of treatment.

Table 3 below compares the costs of long-acting risperidone, haloperidol decanoate, and fluphenazine decanoate at Millcreek Community Hospital in their maximum approved doses for the treatment of schizophrenia.

Table 3 – Comparative Costs of Long-acting Risperidone, Haloperidol Decanoate, and Fluphenazine Decanoate in Their Maximum Doses for Schizophrenia		
Drug/Strength	Maximum Daily Dose	Cost of Treatment per Dose
Long-acting Risperidone/50 mg	50 mg/every two weeks	\$435.05
Haloperidol decanoate 100mg/ml 5 ml vial	400mg/per month	\$19.50
Fluphenazine decanoate/ 25mg/ml 5 ml vial	100 mg/per month	\$2.85

Clearly, long-acting injectable antipsychotics play an important therapeutic role in the management of schizophrenia in those patients with compliance problems. Direct comparisons of long-acting risperidone to other long-acting antipsychotics are not available and the drug is extremely expensive. In the single clinical trial reviewed by the FDA, the drop out rate for

patients treated with long-acting risperidone was 56 percent and most of these were because of an insufficient response to the drug.

Long-acting risperidone may have a useful role in the long-term management of schizophrenia in outpatients requiring second generation, or atypical antipsychotic, treatment who are non-compliant

with oral therapy and are not able to tolerate less expensive first generation agents. The drug's role in the acute psychiatric care setting is unclear and appears not to be needed.

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COMMENTARY IS THE FDA'S ACCELERATED APPROVAL PROCESS IN THE BEST INTEREST OF PUBLIC HEALTH?

The lead article in this issue of *The Drug Information Letter* deals with three related issues: the Food and Drug Administration's (FDA) accelerated approval process, the use of surrogate endpoints as the basis for approving new drugs to treat serious, life-threatening conditions, and the poor compliance of drug manufacturers in confirming a clinical benefit for drugs approved under the accelerated approval regulations.

An emotional, highly charged question may be raised: Is the rapid availability of new drugs that have not been demonstrated to confer a clinical benefit in the best interest of public health?

The FDA's accelerated approval process was spurred by the emerging AIDS epidemic in the mid-

1980s. There were no treatments and thousands of patients were facing a death sentence. Patients and advocates wanted drugs and they wanted them quickly. The accelerated approval process is intended to address this need by allowing the marketing of new drugs shown to have strong effects on measures of biological activity, if those measures are potential surrogates for true measures of a tangible clinical benefit.

The history of surrogate endpoints is checkered. Two classic examples where the surrogate endpoints were unreliable measures of clinical efficacy are:

- The use of arrhythmia suppression as a surrogate for decreased cardiovascular related mortality.^{1,2} The wide spread off-label use of antiarrhythmic drugs to suppress ventricular arrhythmias in post myocardial infarction patients may have been responsible for 100,000 deaths.³
- The use of exercise tolerance in congestive heart failure as a surrogate has shown that some treatments that affect this end point produce improved survival; others provide no benefit or actually decrease survival. Flosequinan (Manoplax), a vasodilator, was conditionally approved by the FDA because it could improve exercise tolerance in patients who did not respond to or

could not tolerate other drugs, including diuretics and angiotensin-converting enzyme inhibitors. The conditional approval required completion of a trial, such as the ongoing Prospective Flosequinan Longevity Evaluation (PROFILE), that could evaluate the effect of flosequinan on total mortality. The PROFILE study eventually provided significant evidence that flosequinan increased total mortality (relative risk, 1.43), leading the manufacturer to withdraw the product from the market.⁴

U.S. Representative Edward Markey of MA in his report on the performance of drug manufacturers in completing surrogate end point validation trials alleges⁵ that the FDA is allowing companies an indeterminant amount of time to complete the required trials and continues to allow some products to remain on the market after a validation trial fails. This is equivalent to allowing these new drugs marketing approval using a lower regulatory standard and is done without informing either patients or prescribers of the lower standard.

Thomas R. Fleming, Ph.D., a well known biostatistician, from the University of Washington, Seattle and a frequent member of FDA advisory committees has recently commented on surrogates and the accelerated approval process.⁶ He believes that the motivation for accelerated approval can be in

conflict with patients' best interest. Fleming notes that companies seeking approval for new drugs view accelerated approval as the easiest way to get their products on the market. Not only does accelerated approval allow companies to get marketing approval much sooner, with lower research costs, and a quicker positive cash flow, it allows these companies to market drugs that likely are biologically active but less likely to provide truly important effects on clinical efficacy endpoints.

Fleming concluded his commentary by asking a series of important questions:

Why is it in patients' best interest to have more drugs from which to choose, if there are less-reliable insights to guide their caregivers and themselves in making those choices? And why is it in patients' best interest to have earlier access to biologically active interventions, if these therapies may be inconvenient to receive, costly, and potentially more toxic than effective? And might earlier access to ineffective treatments delay or chill the development and proper testing of other interventions that really do work?⁶

There are no shortcuts in the pursuit of scientific knowledge. The accelerated approval process coupled with the FDA's failure to ensure that confirmatory trials are completed may, in fact, delay the

answer to import scientific questions. This is hardly in the best interest of the public.

Patients need and deserve better drugs, not more drugs. Each time the regulatory bar for marketing approval has been raised, in return, patients have benefited from better therapies.

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