



Trends-in-Medicine

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By Lynne Peterson

SUMMARY

In the future, the FDA is likely to require companies to begin Phase III or IV confirmatory studies prior to granting accelerated approval, and the FDA will put companies under a spotlight if they don't complete those confirmatory trials in a timely manner.

◆ The FDA has the authority to withdraw drugs that have been granted accelerated approval if they don't complete a positive confirmatory trial, but the agency has no plans to do so and probably won't do so -- unless safety becomes an issue. The FDA also is unlikely to withdraw a drug that fails a confirmatory trial if safety is not an issue. ◆ ODAC is likely to be more reluctant to recommend accelerated approvals in the future.

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FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE

Bethesda, Maryland

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The Oncologic Drugs Advisory Committee (ODAC) held an unusual two-day meeting on accelerated drug approvals. The focus was on drugs that have received accelerated approval but have not completed the required post-approval studies, but officials also made it clear they will require an earlier and more serious commitment by manufacturers (sponsors) to post-marketing trials.

Since the FDA instituted accelerated approvals for AIDS and oncology drugs, 19 NDAs have been granted for oncology drugs, involving 16 drugs; only four have subsequently achieved full FDA approval.

12 Accelerated Approvals Based on Trials with No Concurrent Comparator

Drug (brand)	Company	Generic name	Accelerated approval	Full Approval	Indication
Doxil	Johnson & Johnson	Doxorubicin	1995	No	2 nd line Kaposi's sarcoma
Ethiol	MedImmune	Amifostine	1996	No	Cisplatin toxicity in NSCLC
Docetaxel	Aventis	Taxotere	1996	Yes	2 nd line breast cancer
Camptosar	Pharmacia	Irinotecan	1996	Yes	2 nd line colon cancer
Xeloda	Roche	Capecitabine	1998	Yes	Refractory breast cancer
Doxil	Johnson & Johnson	Doxorubicin	1999	No	Refractory ovarian cancer
Temodar	Schering Plough	Temozolomide	1999	No	Refractory anaplastic astrocytoma
Ontak	Ligand	Denileukin deftitox	1999	No	Relapsed CTCL
Mylotarg	Wyeth	Gemtuxumab ozogamycin	2000	No	2 nd line AML
Campath	Millennium and ILEX Partners	Alemtuzumab	2001	No	3 rd line B-CLL
Gleevec	Novartis	Imatinib mesylate	2001	No	CML
Gleevec	Novartis	Imatinib mesylate	2002	No	Metastatic GIST

7 Accelerated Approvals Based on Randomized Trials

Drug (brand)	Company	Generic name	Year approved	Full Approval	Indication
Zinecard	Pharmacia	Dexrazoxane	1995	Yes	Reduction of doxorubicin cardiomyopathy
DepoCyt	SkyePharma	Liposomal cytarabine	1999	No	Lymphomatous meningitis
Celebrex	Pharmacia	Celecoxib	1999	No	Reduction of adenomatous polyps
Zevalin	Idoc Pharmaceuticals	Ibritumomab tiuxetan	2002	No	Relapsed/refractory follicular NHL
Eloxatin	Sanofi	Oxaliplatin	2002	No	2 nd line colorectal cancer
Arimidex	AstraZeneca	Anastrozole	2002	No	Post-menopausal ER+ breast cancer
Gleevec	Novartis	Imatinib mesylate	2002	No	First line CML

The bottom line at this meeting was that the accelerated drug approval process is getting more difficult, in at least three key ways:

1. The FDA is taking a tougher stance on confirmatory trials. Sponsors will have to have an confirmatory trial strategy from Day One, which a pharmaceutical industry consultant said would require a “sea change in thinking” by sponsors. The regulations establishing accelerated approvals give the FDA the discretion to require confirmatory studies, and it appears the FDA will place greater emphasis on these trials in the future. Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA, said, “The preamble to the accelerated approval regulations comment that post-marketing studies would usually be underway at the time of accelerated approval. Though we haven’t required that...the division believes these studies need to be carefully discussed with the FDA early in the process, a continuous dialogue during these confirmatory trials, and there need to be strategies for alternatives if they fail. We assume confirmatory trials are an inherent part of the approval process...Confirmatory trials should be carefully integrated into the development plan.”

2. The ODAC panel may be more reluctant to recommend accelerated approvals in the future. A consultant said, “It was a shock wave that it could be politically impossible to withdraw a drug with accelerated approval, so an accelerated approval is approval, and that logically changes the standards of accelerated approval.” A panel member said, “My message (from the FDA) is that we should be more careful about accelerated approvals in the future than in the past...In oncology we approve on surrogates without the power of AIDS drug trials, but right now our surrogates are really relatively weak compared to AIDS

drugs...We all feel a need to bring drugs that *may* help people, but *may* is operative word.” Another member said, “It’s become clear that accelerated approval is the same as full approval, so we will have to take a harder look at accelerated approval requests.” A third member said, “We should *never* grant accelerated approval on a subset of patients.” A fourth panel member said, “I now have doubts whether accelerated approval should be given at all.” A fifth panel member said, “The term (accelerated approval) has become real to some of us, and there is a risk here of the pendulum swinging in the other direction. There will be more vigilance by the committee, and maybe a little more reluctance to approve some drugs on the meager evidence which is being presented. There are a number of potential scenarios:

- The slam dunkers – those which zip through with wonderful Phase II trials.
- Those where accelerated approval is followed by a study which is negative and that may be in the same or a different indication.
- The ones that never going to happen.
- The problematic one where accelerated approval is preceded by large negative studies. That is exceptionally problematic.
- Those where the confirmatory trial is negative in a different indication.”

3. The FDA will focus more public attention on what companies are doing to meet confirmatory trial commitments. The FDA plans to put a spotlight on companies that don’t complete their confirmatory studies – with a lot of periodic reviews and additional public advisory committee meetings -- and the Agency warned it could get more aggressive if companies still don’t comply or make a significant effort to comply.

Some panel members appeared shocked at the reality of what accelerated approval means. One said, “I’m struck with the limited data that has been accepted for accelerated approval. It concerns me that I see ‘hints’ of success as adequate for approval...but once the cat is out of the bag, it can’t be retrieved well at all.” Another member said, “Accelerated approval had the idea of getting drugs to patients earlier, but it actually is competing with clinical trials that ultimately help us figure out if these drugs work. God help us if we approve one of these drugs and then -- perhaps by going to Russia (to dot the trial) – we find out a drug actually hurts people. We have had drugs in the past we ultimately found had a net harm...so I think we need to step back and look at the accelerated approval process...Most patients, and I suspect most doctors, don’t understand the difference between accelerated approval and regular approval.”

Some of the confirmatory studies are taking inordinately long to perform, and that worried some panel members. One said, "I'm starting to worry...about the ethics of the time it takes to get these answers -- 10 to 12 years in (one) trial. One of the issues I worry about is the poor patient wasting his efforts in a trial trying to be a good patient and then learning nothing from it. That is an insult to the patient." Another commented, "There is a recurrent theme over these two days: When accelerated approval is given, that allows a drug to market...so the sponsor has money from use. Therefore, if I were a company, I'm not sure I would have the same due diligence toward getting some of the studies done as I would if I were going for full approval. So the very existence of accelerated approval creates a circumstance."

Several panel members also suggested that the term "accelerated approval" may send the wrong message to doctors and patients. A panel member said, "I think the problem is the word 'accelerate'...To most people it means that there probably is a better reason you are allowing the use of this quicker -- it must be better because it got through faster -- and that is the struggle we are having, that people take it that way and act on that." A patient advocate said, "My perception has been that we are talking about drugs that show unusual promise, and that is why they are made available prior to completion of clinical studies. I think that is a widely held perception, perpetuated by the media." Another panel member said, "Some colleagues don't like the name accelerated approval, which does assume the drug zipped through and is moving fast. 'Unconfirmed Approval' might be a better term." A fourth panel member suggested using the terminology "Limited Approval." FDA officials nixed another suggestion, for "Conditional Approval," saying that had been considered and rejected as "politically incorrect."

FDA officials had several messages for sponsors with this two-day advisory committee meeting. These included:

Take confirmatory trials seriously. FDA officials wanted to instill a sense of urgency and to convey that the FDA is taking Phase IV confirmatory trials seriously. Dr. Pazdur said, "The success of the program is not just whether Phase IV commitments have been met...but the initiative behind this meeting is to put the light of day on some of these (accelerated approval) applications. For sponsors who are not here because their applications are too early, we will see them next year or in 18 months. This is not the final meeting on this...There is nothing like sunlight to get people to fulfill their commitments, and that is why we having this meeting...The essence of this meeting is to bring to light that the confirmatory trials need to be an inherent, integral part of the (accelerated approval) program."

The FDA will be scrutinizing companies to be sure they have assigned sufficient resources to complete the confirmatory trials. An FDA official said, "We want to convey to companies that adequate resources have to be devoted to the post-marketing effort, and we will be looking closely at this."

Complete required trials. Not all accelerated approvals require a confirmatory trial, but completion of any requested confirmatory trial is mandatory. An Elan Pharmaceuticals' official (a former FDA deputy commissioner who participated in the drafting of the accelerated approval regulations) pointed out that FDAMA gave the FDA the authority to waive the requirement for a Phase IV confirmatory trial -- and the discretion to decide not to withdraw a drug should a confirmatory trial not be completed or be negative, "The Agency is not compelled to require Phase IV trials. The Agency can choose *not* to require them, but if they do chose them, companies must do them...and the FDA may withdraw approval if a sponsor fails to conduct a study."

The FDA's Dr. Pazdur said, "The regulations state that we *may* ask for confirmatory trials, not that we must...You have to take a look at the total picture...The principle is that it is not necessarily a knee-jerk reaction...But when we ask for them -- which I assure you under my rein will happen -- sponsors are required to do them...I feel passionately that sponsors need to put their full-force behind getting a drug (fully) approved. Once a drug is out there, it is a drug, not a hypothetical drug, so there needs to be an adequate commitment by sponsors that this is a real commitment and should be handled with the same vim and vigor as for a new NDA."

Plan earlier. Sponsors will be encouraged -- or more likely required -- to initiate confirmatory trials earlier in the process, before the accelerated approval is granted. Dr. Pazdur said, "I want trials initiated earlier...I don't want to get dogmatic and say we won't ever do an accelerated approval unless a confirmatory trial is ongoing and enrolled, but I want that to be the exception rather than the rule...The confirmatory trial should be discussed while the Phase II trials are ongoing...and enrollment should "be expected to be nearly completed."

Have a backup plan. The FDA wants companies to have an alternative strategy in place in case the confirmatory trial is negative. Dr. Pazdur said, "In addition to initiating trials early, we should start thinking of alternative, backup plans. Most successful drugs have multiple clinical trials ongoing, and the confirmatory studies are one of many studies...So, we are trying to bring attention to this."

Show safety and efficacy. Accelerated approval does not have a lower efficacy or safety bar than conventional approval. An FDA official said, "There is no different evidentiary level for accelerated approvals."

Consider surrogate endpoints. By law the FDA can accept a lower standard of clinical benefit than usual with accelerated approvals. Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs) said, "We can use surrogates with a drug that serves an unmet medical

need...Surrogates are widely used in other areas like hypertension or cholesterol.”

Beware of withdrawal potential. The FDA has a big stick – it can withdraw a drug if the confirmatory trials are not done or show a safety problem -- but the agency has been exercising restraint in using this authority. Dr. Pazdur said, “I don’t want to deny therapies while trials are initiated, so we’ve allowed flexibility...We don’t want to get into a situation where a sponsor is doing a Phase III trial and claims it is not really a confirmatory trial...Also if a confirmatory trial fails to show clinical benefit, we may then move to remove the drug, and that issue is an area that gives us judgment, so we don’t need a reflex situation where you fail, therefore you must come off the market (for that indication). You have to take a look at the total picture.”

Ultimate responsibility rests with the sponsor. Companies cannot pass off the responsibility for failing to complete a confirmatory trial on anyone else. Dr. Pazdur said, “I encourage interaction with cooperative groups...I’m totally supportive of that...but the obligation to meet Phase IV responsibility rests on the sponsor.” The panel chairman said, “We need a change of mindset by industry. The responsibility is on industry, not the FDA or investigators.”

Some panel members were willing to use withdrawal as a stick with sponsors who do not complete the required post-approval studies in a timely manner. The panel chairman said, The chairman of the panel said, “The feeling from the committee is that, if in the future a Phase IV (confirmatory) trial is negative, and the FDA brings that back to this committee, we would be willing to say, ‘Pull the drug.’”

However, the FDA has no plans to withdraw any of the oncology drugs that have been approved under the accelerated approval process but which haven’t completed a positive confirmatory trial -- unless safety becomes an issue. The FDA continues to be reluctant to use its authority to withdraw an agent that received accelerated approval. Among the comments FDA officials made on this topic were:

- Dr. Temple said, “Accelerated approval comes with a potential – which has never been used today – of accelerated withdrawal. We could come to the advisory committee and seek expedited withdrawal...but you don’t withdraw an active drug lightly. You try to do other studies.”
- Dr. Pazdur said, “Not the drug, but the indication can be taken from the sponsor. That has not been done in oncology or HIV. Obviously, the agency has removed drugs for toxicity, but I’m unaware of any being removed for lack of efficacy.”
- Dr. Temple responded, “Years ago, betahistamine was removed. But the threat is there.”
- Dr. Pazdur added, “Past history cannot predict future trends...It is important to get these therapies out to people

early. We don’t want to undermine people getting therapies early...Studies are fundamental, but they are not the only way we spell the success of the drug. Ultimately, we want to know the answer...but success is more than passing one test.”

- Dr. Pazdur said, “We can take a drug off the market, but that is a very difficult situation. If there is an unrecognized toxicity, we are clearly committed to taking a drug off the market...If push comes to shove, we could take a drug off the market, but then it becomes a highly emotional issue of the past experience with the drug.”

However, the FDA does have a plan to encourage companies to complete successful confirmatory trials. **The Agency is considering granting accelerated approval to competing products unless and until one company receives a full approval.** Dr. Pazdur explained, “A way of encouraging (confirmatory trials) is to let others get accelerated approval in that indication until one drug does prove clinical benefit in an indication., and that is undergoing internal discussion at the FDA...As a carrot, we are contemplating that other sponsors could get an accelerated approval in the same indication until there is a prove clinical benefit.”

Despite all of these problems and issues, FDA officials reiterated their commitment to the accelerated approval process. Dr. Pazdur said, “The FDA believes in accelerated approval. Completion of Phase IV commitments is just one aspect of accelerated approval...We think it is extremely important, but the life of a drug is very complicated...This (meeting) has been somewhat sobering for all of us. You’ve seen our problems – trials not done on time, delays in trials. If these were registration trials, would they have been done faster? A little voice inside me says, ‘Probably so.’”

IMPLICATIONS FOR SPECIFIC DRUGS

ASTRAZENECA’S Iressa was clearly on the minds of the FDA and panel members both days. At one point panel members asked FDA officials what the Agency does when confirmatory trials have already been conducted before an accelerated approval decision is made and the results are negative. Dr. Temple said, “You just saw a case like that, and no one can tell you the outcome. If that (Phase III trial) is how you were going to do the confirmatory trial, you are in considerable difficulty, and then you will have to figure out how to do a confirmatory trial, and that is difficult...Circumstances in which things don’t work out are always somewhat ambiguous.” Dr. Richard Pazdur, Director of Oncology Drug Products at the FDA, said, “You have to figure out why the drug failed That doesn’t mean the drug didn’t work. It could have been inadequate power, stratification, a whole host of design issues.”

There were even direct references to the Iressa situation during the discussion of Wyeth’s Mylotarg, for which a toxicity issue

arose after accelerated approval. Dr. Pazdur said, "It is difficult to characterize safety in single arm trials in refractory patients – like the Iressa situation." Later, in discussing post-marketing surveillance of toxicity when drugs receive accelerated approval, he commented, "The Iressa situation is another example. We have information from Japan, which is more complete reporting on the use of drugs than we do in the US, but it is a real problem." Near the end of the two-day meeting, Dr. Pazdur commented, "Anything that could bear on a decision, especial if it is the same or a related indication, absolutely needs to be presented because it would bear on our decision – and we did that and that data was presented in the case of Iressa."

Six panel members were asked about the outlook for Iressa. Two said that if they were voting now, they would change their Yes vote to a No vote. The others said they would still vote the same way they did.

PRO

- "I think the FDA will approve Iressa. The Iressa toxicity has not changed the risk:benefit analysis. Iressa is no more toxic than other agents used to treat this cancer. The interstitial pneumonia is still rare. But Iressa will get a strong label to warn doctors and patients."
- "I would still vote in favor of approval for Iressa. If the risk (of interstitial pneumonia) is <1%, the benefit outweighs the risk."

CON

- "If I were voting today, I would change my vote and would vote against approval. I don't think the FDA will approve Iressa and they may call another meeting of the ODAC panel to explain why... A Phase IV trial would be very difficult to conduct, and safety is a bigger issue than previously thought...The Phase II data suggested a 12-13% response rate with Iressa alone in patients who had failed two prior regimens. Why doesn't it work with chemotherapy but works alone? Does it really work alone? The company claimed 14% response rate and a 30% improvement in quality of life, but those patients were taken off chemotherapy and given Iressa, and just stopping chemotherapy improves quality of life. The Iressa panel was a very difficult panel. I changed my thinking four times that day and finally voted for approval. Two days after we said Iressa was safe and effective, the Japanese toxicity issue came up. I'm still not sure why AstraZeneca didn't tell the panel about that."
- "I voted in favor of approval, but based on the definition of accelerated approval, I would now vote no...Marginal data led to the recommendation, and the Phase II was negative. Everyone said Iressa had no toxicity, and now we know there was toxicity in Japan."
- "I voted against Iressa at the panel, and I feel even more strongly about that now that the Japanese toxicity has come out."

- "I voted *No* before, and now I am adamant on *No*."

It does not appear likely that the FDA will ask for a second panel on Iressa. The next scheduled meeting of ODAC is in June 2003, but the PDUFA data on Iressa is May 2003. Asked generally about the chances of a second panel on an oncology drug, an FDA official said, "I can't remember a second panel on safety in oncology. It is possible if there were a big concern, but it is unlikely." Another official said, "With accelerated approval, a second panel would be unusual."

Reading between the lines, and considering the comments of panel members and FDA officials, it still possible the FDA may approve Iressa but has not been able to come to agreement with AstraZeneca on design of the Phase IV confirmatory trial. While safety has become an issue, it does not appear to be a barrier to accelerated approval. In oncology, the benefit simply must outweigh the risk. However, it would not be surprising if the FDA asked AstraZeneca for more trial data before approving Iressa.

IMCLONE'S Erbitux also was a topic of discussion both directly and indirectly. A speaker from a patient-advocacy group urged approval or Erbitux, citing anecdotal evidence of significant patient response – including his own wife. FDA officials hinted that Erbitux may qualify for accelerated approval even if Iressa is approved first.

- A panel member wondered, "We came into a situation not too long ago -- and we may again in the future -- with two first-of-class compounds...If one gets approved, and the other comes up six to 12 months later, what happens then? There is no longer an unmet medical need. If both are highly effective, how do you deal with that?"
- Dr. Temple said, "The answer will come soon. We are working on that. The intent was not to kill off appropriately started drugs. We are looking at the current regulations, and I can't say more."

THE PATIENT PERSPECTIVE

Steve Wallace, an official with the Abigail Alliance for Better Access to Developmental Drugs said the experience with accelerated approval has been less than ideal, from a patient perspective, "The result is an accelerated approval program that has not lived up to expectations. We're not seeing enough drugs come through the system." He said this is due to:

- Inconsistent support of accelerated approval.
- Insufficient communication that has not been sufficiently open and real time.
- Limited regulatory acceptance of surrogate endpoints.
- Unrealistic risk:benefit and clinical benefit evaluations.
- Lack of flexibility.

- Sense of urgency rarely evident.
- Some “timely” approvals, but too many delayed.
- Inconsistent usefulness and implementation of Phase IV trials.
- Too much reliance on statistics and process.
- Over-emphasis on adverse events.
- Failure to recognize patients’ rights and ability to make decisions about how they try to live.

He urged the FDA to:

- Accept and support not just the letter of the law but also spirit of the accelerated approval intent.
- Not move the standards for accelerated approval closer to the standards for full approval.
- Redefine clinical benefit to more realistically serve patients with life-threatening diseases.
- Defer more decision-making to the physician and patient in the post-accelerated approval setting.
- Recognize the urgent need for timely approvals, not just timely reviews.

Wallace also urged adoption of a new tiered approval system to deliver medical advances to seriously ill Americans who are being abandoned by the current system: Tier 1 would be a new, initial approval. Based on limited evidence of safety and efficacy adequate to support a determination that the treatment represents the best available care for patients with a terminal disease and no other options. It would restrict approval to treatments for a life-threatening disease and no approved treatment options.

MISCELLANEOUS COMMENTS DURING THE MEETING

- Asked by a panel member how the FDA decides which drugs to bring to an advisory committee, an FDA official said, “We used to bring almost everything to the panel, but I think we are being more selective now because we are getting more me-too type drugs...When we have somewhat borderline evidence and want a judgment of what is reasonably likely, that fits well to taking it to an advisory committee.”
- It appears the FDA attitude may be softening toward the use of time to progression as an endpoint in oncology trials. Dr. Temple said, “We will be back (to the committee) for more discussion on TTP.”

SPECIFIC DRUGS DISCUSSED BY THE PANEL: ACCELERATED APPROVALS THAT HAVE NOT GOTTEN A TIMELY FULL APPROVAL

The advisory committee reviewed all eight of the accelerated approvals granted prior to 1999 for which full approval has not been granted. They are:

JOHNSON & JOHNSON’S Doxil Taking way too long but making an effort

Doxil (doxorubicin hydrochloride liposome) was granted two different accelerated approvals in two different indications. First, in 1995, it was given accelerated approval to treat Kaposi’s sarcoma in AIDS patients with disease that has progressed on prior combination therapy or in patients who are intolerant to such therapy. To date, J&J has not completed a successful confirmatory trial. The original Phase IV trial was before accelerated approval, but when it was completed, the FDA issued a non-approvable letter. *The FDA’s concern with Doxil for this is that the confirmatory trials have already taken eight years, and it may be 2009 before those trials are completed.*

J&J has been working on designing another Phase IV commitment trial, and it had discussions with the FDA as late as last month on study design. A JNJ official said the company is committed to implementing a new Phase IV trial, but said there are substantial barriers to overcome. He outlined some of the problems with Phase IV trials of Doxil:

- The incidence of Kaposi’s sarcoma (KS) has sharply declined with the introduction of HAART. KS has become an “ultra-orphan” indication, with only about 1,500 patients meeting the criteria in the U.S. last year. A panel member commented, “There are enough patients to do a trial; 1,500 patients (a year) is not justification for not doing a trial.” Another panel member said, “In reality, there is no clear-cut plan to achieve assessment in a timely way. Is this not then a basis for withdrawing approval (of Doxil)?” However, there seemed little support for withdrawing Doxil among other panel members or FDA officials.
- Doxil is regarded as standard of care when systemic chemotherapy is appropriate.
- Protocol design has been difficult.

Then, in 1999 Doxil was granted accelerated approval in ovarian cancer. Two confirmatory trials will be available that may help answer the questions about this indication for Doxil.

- Study 30-49. Analysis of the survival data is currently underway on this trial, comparing Doxil and topotecan, and should be submitted to the FDA soon. The primary endpoint is time-to-progression (TTP). A change in the primary endpoint delayed this trial, which began in 1997, and patients in both arms of Study 30-49 have lived longer than expected, which also has delayed completion of the trial.
- SWOG S-0200. This 900-patient study is a comparison of Doxil vs. carboplatin. The first patient was enrolled in September 2002, and the last patient is expected to be enrolled in 2007, with final results in 2009.

LIGAND'S Ontak

Taking way too long but making an effort

This fusion protein, which has orphan drug status, received accelerated approval for persistent or refractory CTCL in 1999. A Phase IV trial, L-4389-11, of Ontak (denileukin diftitox) has been underway for more than a decade. The goal is 195 patients, and 105 been enrolled so far, with a primary endpoint of response rate and TTP. There are three arms in the trial: 39 patients on placebo, 78 patients on up to 8 course of 9 µg/kg/day, and 78 patients on up to 8 courses of 18 µg/kg/day. Enrollment has picked up in the last nine months, and the sponsor has been enrolling more sites outside the U.S. The target for submission of a final study report is early 2006. ***The FDA's concern is that this drug has already been studied for 10 years and it will be at least another three years before it could get full approval.***

The challenges in conducting this trial include:

- Small population size. There are only about 1,100 new cases diagnosed each year in U.S. About 400 patients got Ontak commercially for CTCL last year.
- Impact of prior therapies on eligibility. It is hard to find naïve patients, and the company is concerned that loosening eligibility requirements would invalidate the results of the trial.
- Impact of the placebo arm. Patients and investigators often decline to participate, and the French government declined the clinical trial application citing the revised Declaration of Helsinki. An Ontak researcher said, "Once Ontak was approved, it was very difficult to get patients into this study...to expect a patient to stay in a placebo arm where they are not getting benefit for eight cycles is a lot to ask because patients are all symptomatic or we wouldn't be treating them."

Panel members did not appear worried about the delay in this confirmatory trial. One member said, "I find a lot of good news here. We see a sponsor getting a lot of information from a hypercritical review. I think they have tried, and we have an orphan drug, and when you are dealing with an orphan indication with <100 patients presenting a month, they are doing their very best and should be commended." Another said, "This is a drug that appears to have benefit in one-third of patients with an uncommon disorder...The trial is having trouble accruing for a number of fairly valid reasons. Virtually everyone would like the integrity of the study to be maintained as long as possible...and there was some encouraging news on accrual recently." A third panel member said, "I would encourage the trial to continue rather than shut down and re-think the design."

MEDIMMUNE'S ETHYOL

Taking way too long, negative confirmatory trial, and safety concerns

The Phase III post-approval trial for Ethyol (amifostine), Study WR-0053 in Stage IIIb or IV NSCLC, was ongoing at the time of accelerated approval. That study had mixed results.

Study WR-0053 was one of five Phase III trials the sponsor has conducted. A company official said, "We don't see anything to suggest an (negative) overall survival issue with amifostine...Nephroprotection was confirmed...but WR-0053 did not meet our accelerated approval obligation...The FDA says we still need to do another study demonstrating nephroprotection and non-inferiority of survival or a survival surrogate."

Results of Amifostine Study WR-0053

Measurement	Amifostine + cisplatin	Cisplatin
Nephrotoxicity	28%	49%
Tumor response rate	30%	32%
Mean progression-free survival	4.14 months	4.73 months
Median survival	8.75 months	9.3 months

MedImmune has two problems with completing a new trial:

1. **Size.** An official complained that a non-inferiority trial would require 2,400 patients if survival were the endpoint, and 1,150 patients if response rate were the endpoint. To demonstrate nephroprotection alone would take 400 patients. He estimated a large trial would take ≥6.5 years to complete.
2. **Accrual.** There is a changing pattern of cisplatin utilization with decreased use of the high dose regimen, and carboplatin is being substituted more frequently for cisplatin.

MedImmune appeared to hope that the committee would recommend that another trial should not be required, but they got little support for that position. An FDA official said the agency has serious concerns that the drug could be tumor protective, "One of the problems with this application on tumor protection is that our approach and knowledge of this field has progressed and tumor protection is one issue and non-inferiority is another issue...both of those are of concern to us...You really do need to prove you are not protecting the tumor...that's why we stuck to our guns on this one and are not going ahead without proof...I don't understand why this drug should protect only the patient and not the tumor...You need to at least know what effect the drug has...and to be sure that if the drug wasn't there that you would see a difference. That is the minimal standard...We are not really asking for a very strict non-inferiority trial, just a gross indication the effect has been retained."

A panel member even questioned the nephroprotective effect. He asked MedImmune officials, "We focused on protection against nephrotoxicity at a higher dose, but the sponsor said lower doses are more commonly given. What is the magnitude of nephroprotection at the lower dose?" A MedImmune official responded, "We don't have that information...Those studies were not performed."

After the meeting, a MedImmune official indicated the company will now reassess what to do. Company officials plan to meet with FDA officials to discuss possible new trial designs.

SCHERING PLOUGH'S Temodar

Strongly criticized for taking too long and apparent lack of commitment to completing the confirmatory trial in a timely manner

Temodar (temozolomide) was granted accelerated approval in 1999 for treatment of adult patients with refractory anaplastic astrocytomas, based on a single-arm study of 62 relapsed patients that showed a progression free survival of 51% at six months, a median survival of 13.6 months, CR of 5% and PR of 28%. The FDA did not feel the tumor progression data was sufficient for approval, but the FDA approved the drug based on a subgroup analysis of patients. Schering made a post-marketing commitment, but a final report is not expected until June 2007, and safety concerns have been raised.

Part of the delay has been due to complications arising from efforts to work with a cooperative oncology group. A panel member found that excuse plausible, saying, "The sponsor went to a cooperative group, and then was criticized because the group wanted to add an arm to the trial. With cooperative groups, something that comes out is often better than what went in...I can't fault the sponsor for going to a cooperative group. Often the group says it is more scientifically interesting to do something another way." However, Dr. Pazdur still put the responsibility on Schering, "I encourage interaction with cooperative groups...We encourage the participation of sponsors with cooperative groups, both on registration and risk education trials, and adjuvant trials...I'm totally supportive of that...*but* the obligation to meet the Phase IV commitment rests on the sponsor."

The FDA is concerned that Schering has not made a serious and timely commitment to a confirmatory trial. In fact, Schering officials were very strongly criticized by Dr. Pazdur. He had sharp words for the company, saying, "I'm personally unhappy...We have a drug approved in 1999, and we are first getting started with a confirmatory trial in 2003. I think that points out real big problems...We have to start thinking of development plans here, not just a step-by-step, narrow approach to drug development. How could we have improved this picture?...Whose responsibility is it to do the Phase III trial? It is the company's responsibility, and I really want to send that message to you – a public record. It is the

company's responsibility to have a plan that fits FDA standards...You have a drug out there. The company is obviously is making a profit. There is a real drug. What should the commitment of the company be in terms of multiple studies? What is the level of proof? We always insisted sponsors should do two trials...in case one fails, has methodological problems, or has accrual problems. I fully understand when companies are not sure of approval and have to be careful on expenditures, but here is a known drug and there should be a willingness to invest...It is truly unacceptable that the company is now just beginning a trial and accrual is poor...And the EORTC (European) study is not being done under an IND, and I am very unhappy about that. I would especially want to publicly criticize you for not doing that...You have not met your Phase IV commitment."

WYETH'S Mylotarg

Taking too long, new safety questions, and lack of backup plan in case confirmatory trial fails

Mylotarg (gemtuzumab ozogamicin) was approved in May 2000 for treatment of CD33⁺ AML. There are about 10,000 people a year who get this disease, and about 300,000 people in the U.S. with it, making it an orphan indication.

A confirmatory trial is underway, but the data is not expected until 2011. The drug has not yet been approved in Europe.

The company cited several challenges to completing its confirmatory trials, including:

- Uncommon disease.
- Recruitment problems. Treatment typically at major med centers and universities, so there is a need for cooperative group participation, but many of the groups have declined participation.

In the NDA submission, a 2.1% incidence of liver function abnormalities was reported. Since then, higher rates have been reported. In an observational study that is ongoing, the rate currently is 4.4%.

FDA officials are not happy with the progress of the confirmatory trial. One FDA official said, "Accrual has been less than dramatic. (Recently), there's been a remarkable jump in accrual, and (jokingly) I'm sure had nothing to do with this meeting." Another official said, "It seems to me that your Phase III trial is not likely to be successful...In the past 15 years, no one has improved on the two drugs we already have. If you fail, then we will be asking if we should still (allow) this drug."

FDA officials also are concerned about the safety of Mylotarg. An FDA official said, "It is difficult to characterize safety in single arm trials in refractory patients and this is an example of that...Wyeth was very cooperative in coming up with a plan to keep an eye on this veno-occlusive disease (VOD), and we came up with several responses to this

(labeling and a black box warning)...In our EROS data base, we reviewed 125 reports of liver toxicity associated with fatal outcomes...This is illustrative of the challenges we face when we approve a drug...It is like opening Pandora's box."

The panel also had concerns. The committee chairman said, "The sponsor has made an incredible effort in accrual...This is the poster child of all the problems that can happen, but Wyeth has come to the forefront with solutions as well." Another panel member said, "I'm pleased to see the design of a Phase III that could provide considerable insight on the role of Mylotarg in first line therapy, and I truly hope for positive results and a survival advantage...but there is a very real possibility it won't be positive, and we will have taken 10 years...The concern is that if the trial is negative, we are left with a number of uncertainties...We haven't established benefit, just a marker that is reasonably likely to predict clinical benefit. It is certainly not out of the range of the possible that Mylotarg won't provide a benefit...I'm troubled by what appears a very open-ended situation."

SKYEPHARMA'S DepoCyt

Taking too long and concern it may not be efficacious, although it is a gentler method of administration

This drug has been in development for 11 years, and was granted accelerated approval in 1999 to treat lymphomatous meningitis, a cancer in which patients typically die in about 38 days. A confirmatory trial was started after accelerated approval, but then the drug was recalled from the market due to manufacturing problems. The trial recently resumed, but accrual is going slowly, and the trial is not expected to be completed until 2004.

One of the challenges in completing this trial is that it is impossible to blind the trial, and the DepoCyt delivery method and schedule is much gentler for patients than the other two available therapies. The question is whether the drug has benefits other than a quality of life benefit. Unfortunately, it would require too large a trial to prove non-inferiority, so the company has to show a benefit, not just quality of life.

The FDA is concerned that the Agency still does not know if this drug really works. An FDA official explained: "I have praise for the design of this trial...(but) accelerated approval was not intended to be an alternative for a product, which would not fulfill the criteria for full approval, coming through an alternative mechanism. DepoCyt was approved on a relatively modest number of patients...Because there was a suggestion of potential utility, the committee recommended they get accelerated approval...We still don't know the utility of this product and it is approx 16 years since the filing of an IND."

The FDA has worked with the sponsor to prove the value of this drug. An FDA official said that, since the drug did not appear to affect survival, "We were willing to explore time to

neurologic progression...We were interested in looking at whether there is a symptom benefit, a quality of life-type of endpoint for product approval...We worked with the sponsor in essence in uncharted territory...Here is an experiment where we are the neutral observer or judge, provided that we are given thorough and adequate documentation to make that assessment...We hope the study will be informative. If we can't tell a difference, I believe the committee would revisit this application – which would be approximately 18-20 years after the IND was filed."

The panel was not concerned with Skye proving superiority. A panel member said, "To me this drug doesn't need superiority, just that it is not worse than anything else...The very fact you can give it less often is an exceptional advantage, so standard to which we hold this is key to me." Another panel member said, "I think the sponsor has been vigilant...There have been some accrual difficulties in the past that appear improved by the addition of some European centers...The fact that the trial was extended to Europe will help because it is not approved there." A third panel member said, "I think it would be unfortunate to lose this drug if it is non-inferior. It has a tremendous impact on quality of life, so it is unfortunate if the trial can't be non-inferiority."

PHARMACIA'S Celebrex

Taking too long

Celebrex (celecoxib) received accelerated approval in 1999 to treat familial adenomatous polyposis (FAP), a rare, life-threatening genetic disease that accounts for 1% of all colorectal cancer (CRC) in the U.S. If untreated, there is a 100% CRC risk and a median life expectancy of 42.

This is a little different from the other agents discussed because it is a pre-malignancy treatment. Celecoxib was shown in pre-approval studies to reduce polyp formation. The question is whether reducing the number of polyps actually reduces the cancer risk. The idea is plausible but controversial. A panel member said, "I think (the company is) doing what it can do. I think we will eventually get a Phase III...I think the sponsor has made a strong effort to meet the Phase IV requirements." Another panel member said, "The realization that 100% of these patients will progress to CRC if untreated, and with a documented 28% reduction in polyp formation, makes me think we are more impacting the timing of the occurrence of CRC than ultimately influencing the occurrence of CRC...I agree with the FDA that much more needs to be understood about the clinical benefit...and the randomized trial is an interesting piece...Yet, clearly so much more needs to be understood, that a registry is critical." A third panel member said, "It would be great if it prevented cancer...but this population gets colostomies as teenagers...so just delaying that until they finish school is psychologically beneficial and extremely important. Even if it only delays colorectal cancer, that is very important."