

Strategies for Gaining Cancer Drug Approval

By Sandra Holtzman

What should sponsors and analysts/investors be looking for in the upcoming 2007 season? A panel of experts reveals their opinions and ideas.

The recent “Building a Successful Cancer Development and Registration Strategy” workshop at the 2007 Bio Investors Forum held in San Francisco, offered good advice on what sponsors and analysts/investors should be looking for in the 2007 season. Goals of the workshop included helping companies/sponsors avoid costly mistakes which can threaten the progress or even existence of new products; and to assist investors by helping them determine which of the 400 drugs—and the companies that produce them—are worth betting on. Speakers noted the importance of clinical trials, because trials reveal critical information on which investing decisions can be based.

Themes the presenters considered included dealing with reimbursement issues while still

in clinic, recognizing and side-stepping potentially expensive and time-delaying pitfalls, critical elements that need to be included in designing successful clinical trials, and dealing with different regulatory agencies.

Reimbursement Issues While Still in Clinic

Robert J. Dow, MBChb; Senior VP, Medical Affairs, at Cell Genesys, Inc. advised that key issues such as reimbursement be examined early on in determining which drugs to pursue through the pipeline and how the drugs will likely be affected by the reimbursement process if approved.

The primary list of tasks Dow recommended a company to consider included:

- Developing an understanding of likely



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reimbursement in all major markets—not only in today’s environment but in the future as well.

- Considering the needs of the stakeholders—the policies makers, payers, physicians, and patients.
- Identifying appropriate clinical and pharmacoeconomic data.
- Looking closely at coding (particularly in the US).

He also discussed how the reliance on pharmacoeconomics is essential in negotiating formularies in agencies such as Medicare, Medicaid, managed care, and the VA. He advised on establishing billing codes and making sure codes are planned for far in advance. “It takes quite a long time in getting these codes,” stated Dow, if a company’s product doesn’t fall under an already existing one.

With \$50,000 a year as the worldwide (currently) accepted trigger point for cost of drug, “make sure you’re below that number,” says

Dow. This data is best obtained during Phase III trials—and can be accomplished during the trial with minimal extra expense. By doing this research while still in trial, the company can use the results and plan pricing in advance of approval. Many people in the industry agree that this will become increasingly important in the future.

Recognizing and Side-stepping Pitfalls

Current research trends and issues in targeted biologics versus chemotherapy was discussed by Hope Rugo, MD, Clinical Professor of Medicine, Director, Breast Oncology Clinical Trials Program, University of California, San Francisco Medical Center.

In drugs developed too quickly, it takes a long time to understand their pharmacokinetics. Using taxol as a case in point, Rugo discussed how it took researchers more than a decade and thousands of patients in clinical trials to discover that the drug is more effective when administered every week as opposed to every two weeks. Because taxol’s pharmacokinetics was better understood, its use was increased.

Rugo further discussed that clinical trials can be designed based on molecular profiling. By looking at molecular profiling, and how profiling correlates with outcomes, researchers may be able to separate **cont. on pg 38 >>**

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different subtypes of cancers to see results sooner. By targeting patients who are doing poorly in trials early on, researchers might see a big difference in outcomes, but they have to know what they're targeting and then target the right endpoint.

Rugo also discussed what he calls repackaging old friends—taking the drugs already in use and making them more effective and less toxic. In the case of paclitaxel, the toxic solvent (which caused nerve damage) was removed and replaced with a water solvent. The agent was then repackaged in an albumen or protein shell. Albumin is an active transport mechanism of nutrients. The result is that patients have greater exposure to the drug per dose, no pre-medications are required and the infusion time is 15 minutes.

Rugo predicted a future that uses a combination of treatments (i.e. combining chemotherapy and targeted therapy), but warned that targeted biologic therapy is not less toxic than chemotherapy alone.

Rugo also warned companies to make sure that the right population of patients is targeted when doing studies with new products. Many trials of the sort Rugo discussed have to be open-label and therein resides the issue of the FDA using the data obtained from the trial for registration.

Identifying Critical Elements in Designing Successful Clinical Trials

Richard Dean, PhD, CEO Xanthus Pharmaceuticals, Inc. used a case history of acute myeloma leukemia (AML) to demonstrate steps to take for a successful registration study. When positive results were seen in a Phase I study, Xanthus decided to move forward.

In further trials, patients included those who

had relapsed AML and those with secondary AML. Patients had no alternative therapy at their therapeutic stage. "This is a great clue," stated Dean, "as there was a complete remission rate of 12 out of 21." Complete remission can be a valid primary endpoint for the FDA. This is an example of identifying a critical element towards creating a successful trial design.

An unmet medical need (defined in this case as complete remission) and no current drug labeled for AML afforded an opportunity for accelerated approval in Dean's case study.

In his example, the primary endpoint was complete remission which can be determined within 30 days—getting to that endpoint fast sped the approval process.

Successfully Dealing With Different Regulatory Authorities

How do companies communicate with the FDA? What do companies mean when they tell analysts they've spoken to the FDA? Greg Berk, MD, Senior VP, Chief Medical Officer, Hana Biosciences delved into this critical issue.

Berk resonated with other panelists that open-label trials are becoming more frequent as more combinations of treatments are becoming available. The combinations are posing difficult registration issues. "I don't know of a case of the FDA approving a drug in an open-label trial. I'd be very curious about how it's done."*

According to Berk, a key issue for achieving FDA approval is making sure that the company/sponsor follows FDA directions. "A lot of companies are told things by the FDA and they come back without having done it." This

...clinical trials can be designed based on molecular profiling.



is how companies fail to get approval.

In the case of biotech companies, which are small, not following FDA directions can be particularly damaging. Biotechs can't afford to absorb the cost of delay or approval failure, particularly if they have no existing revenue stream. Additionally, there's enough of an inherent risk of compound failure generated by a trial without a company having to aggravate the risk by not adhering to FDA directions.

Below are key points Berk advises to keep in mind when developing a clinical trial. Questions a company may want to ask itself include:

- What defines a good drug?
- What is clinically meaningful about the drug?
- What's the drug's indication going to be?
- What is a valid endpoint in your trial?

"The FDA wants to know where you are going especially when you are developing a drug for a niche indication. You need to present your entire pathway," says Berk.

It is very important to make sure that your company and the FDA are in synch with the issues of what defines clinical benefit and what a valid endpoint is. Companies should bring their strongest people to a regulatory meeting and make sure their rationale for conducting a trial is clearly expressed.

Other points Berk made included to stay in touch with the FDA—the more in touch a company is, the better their review is going to go.

Don't waste the FDA's time—FDA doesn't appreciate putting together a team of 10 to 15 reviewers when a company isn't focused on the endpoints of their trial.

Have a sound clinical trial design in place.

"If you are going to do an open-label, accelerated, questionable endpoint, combination, it's very wise to make sure you have some kind of agreement in place with the FDA before you start the trial."

Berk noted that the FDA got a record number of requests for meetings last year; and that many companies are mistakenly thinking they can use the FDA as a publicly-funded consulting firm. The agency will not tell a company where to take a drug based on trial results. That's the company's responsibility. "You need to show them [FDA] your pathway, and have focus, not ask them. There should be a very specific set of detailed questions with an ultimate goal to get an NDA approved."

Berk also noted that there is a wealth of published guidance available about this subject.

Know when a Special Protocol Assessment (SPA) is a good idea and when to take advantage of the process. SPA's might be used if a company is going for a non-traditional type of approval, (i.e. if a trial is non-randomized). This process provides some degree of assurance of eligibility, but it's not assurance of approval.

"It's an agreement that your most critically important pieces of your trial design are in place and that your end goal is agreed upon [with the FDA] and if that is met there's a good chance, not a guarantee, for approval," says Berk. The downside of using an SPA is that it can affect your time line. **SH**

* NOTE: OBR contacted the FDA to clarify open-label trial issues and was told by Robert Justice, MD, Director, Division of Drug Oncology Products, that "many oncology drugs are approved based on open-label trials. Blinding of a trial or an independent blinded review of endpoint is needed only when the primary efficacy endpoint is open to bias." Dr. Justice further recommends "an end-of-Phase II meeting with FDA...prior to initiation of Phase III trials."