



A Tale of Two Cancer Immunotherapy Companies

Same tumor target, parallel development, and very different approaches



Delivering patient-specific therapies represents a fundamental shift in how cancer is being treated. The next two years are expected to be crucial to the development and commercial viability of Genitope's MyVax[®] and Favrille's FavID[®] NHL candidates.

Two companies, Favrille, Inc. and Genitope Corporation, have reached Phase 3 development with custom-made, patient-specific immunotherapy compounds to treat non-Hodgkin's lymphoma (NHL). While there are similarities between the two products, there are also several striking differences, notably each company's proprietary technology and manufacturing processes and the intended clinical use of their products, i.e., whether the product is administered following a Rituxan-induced remission or a chemotherapy-induced remission. As both companies near market approval in the next 1 to 2 years, these differences may or may not play a significant role in the commercial viability of their products, and even the companies themselves.

Technology and Manufacturing

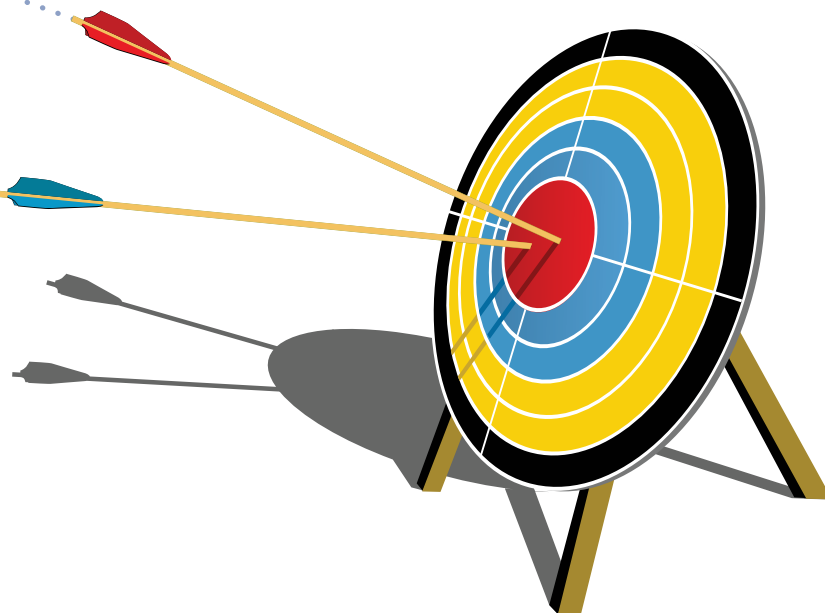
The clinical data supporting R&D in B-cell NHL dates back to the late 1980s, when a few small-armed, observational clinical studies at Stanford and the NCI found that antibody being produced by a lymphoma could serve as a target for a personalized, active immunotherapy. Despite these exciting findings, manufacturing and commercial-scale production of active immunotherapy involved a difficult, time-intensive process. However, companies such as Favrille and Genitope set out to develop techniques and manufacturing processes to address and overcome these obstacles.

Favrille begins its manufacturing process with biopsy tissue from a patient. From the tissue, genetic information is extracted that is specific both to the patient and to the idiotype protein being produced on the surface of the patient's lymphoma cells (see Figure 1).

"What is particularly unique about Favrille and allows us to efficiently produce a personalized immunotherapy product is the use of a baculovirus [non-mammalian] insect cell expression system," said John P. Longenecker, PhD, Favrille's President and CEO. This aspect of the process saves production time, resulting



By Michelle Nolin Flewell



in an 8-week throughput from biopsy to personalized product.



John P. Longenecker, PhD
Faville President and CEO

Next, Faville makes the idioype protein specific to the patient's tumor immunogenic, which is achieved by conjugating it to keyhole limpet hemocyanin (KLH), a highly immunogenic protein used for decades as a vaccine adjuvant. The resulting personalized, active immunotherapy, FavID[®], is co-administered to the patient with the immune system growth factor GM-CSF which activates dendritic cells at the injection site and further stimulates the patient's immune response.

"We've created a target that is very specific to each patient's tumor, and made a product that will create an immune response targeted against only tumor cells in that patient, thereby training the patient's immune system to attack the tumor he or she is carrying," said Dr. Longenecker.

FavID and GM-CSF are co-administered subcutaneously once a month as induction therapy. If a patient responds and tumor does not progress over 6 months, patients convert to a booster program where drug is administered every other month for a year. If patients remain in remission, the booster regimen is continued once every 3 months until disease progression or relapse occurs.

Simultaneously, Genitope's lead product for NHL is the active idioype vaccine MyVax[®] Personalized Immunotherapy (formerly known as GTO-99). Similar to Faville's lead candidate FavID, MyVax uses KLH as the carrier protein for the idioype protein and it is administered with GM-CSF as an adjuvant (see Figure 2).

Genitope uses a propriety technology called Hi-GET that allows rapid, efficient generation of mammalian manufacturing cell lines.

"Similar to other biotech firms that manufacture monoclonal antibodies from a mammalian cell line for each antibody, we are able to generate a patient-specific product [cont. on pg 30 >>](#)



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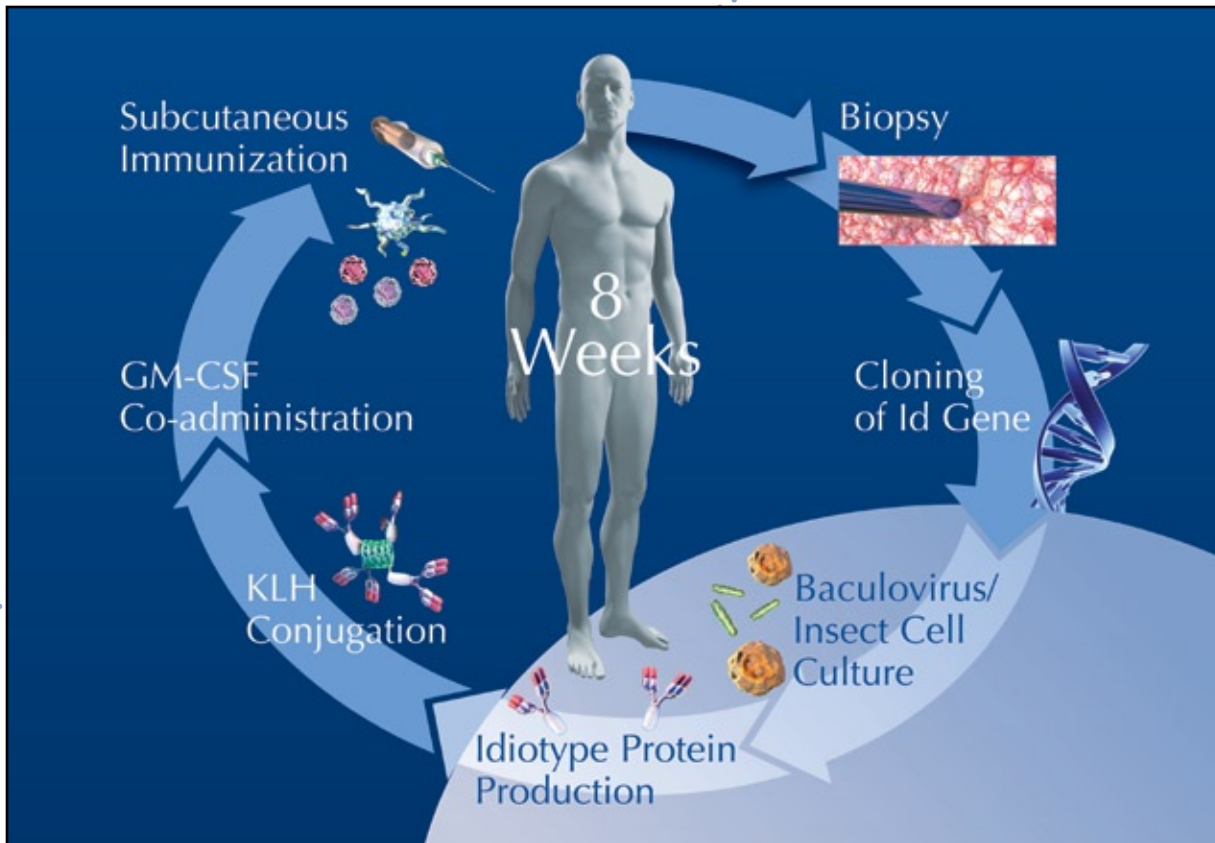


FIGURE 1: Faville Manufacturing Process. Reprinted with permission from Faville Corporation.

for each patient enrolled in our clinical trials, and in a commercial capacity, we'll likewise be able to manufacture patient-specific immunotherapy once our product is approved," said Genitope's Chairman and CEO Dan W. Denney, Jr., PhD.

Genitope anticipates that scale-up will not be difficult, noting that the problems with commercial-scale manufacturing historically involved inefficient technologies with a number of non-commercial characteristics. "Once we had determined our commercialized technology, we got over the hump of being able to turn our research into a business," said Dr. Denney.

Genitope estimates the throughput for MyVax—the time from biopsy to production—to be approximately 3.5 months, including all required FDA release testing, sterility tests, QA, etc. Dr. Denney added that the time to product development will vary from one patient to another, as some individual tumors are more difficult than others; for example, a personalized product to treat a difficult tumor can take as long as 6.5 months to develop.

Two Approaches for Immunotherapy Products for NHL

Amid the revolution of lymphoma treatment in the late 1990s as a result of the launch of the

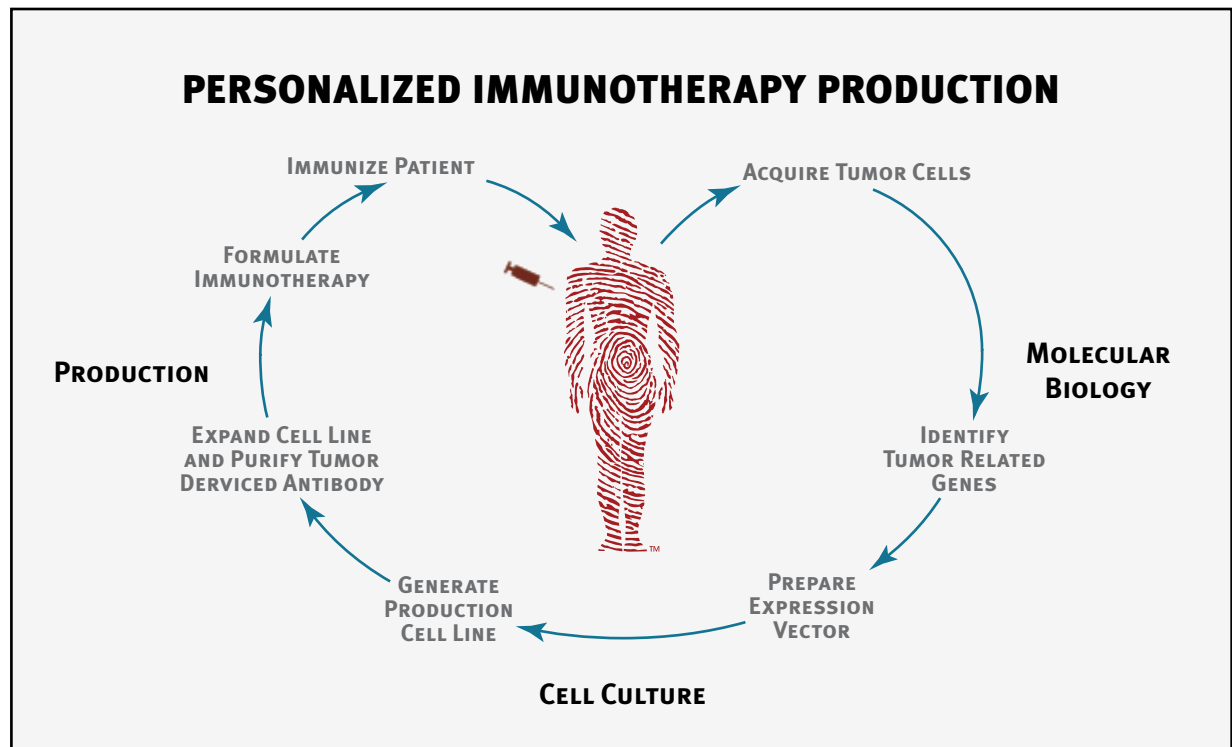
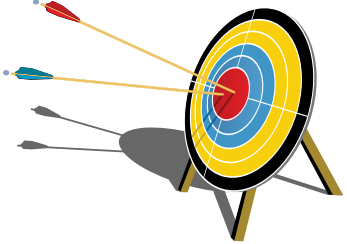


FIGURE 2: Genitope Manufacturing Process. Adapted from Genitope Corporation.

passive immunotherapy agent Rituxan® [rituximab; Genentech], Favrilie devised a clinical trial strategy that differed from other trials of active immunotherapy candidates, pursuing the use of their product as an adjunct to treatment with Rituxan.

In Favrilie’s clinical trial setting, patients receive Rituxan first (a one-month course) to induce remission, and 2 months later begin induction therapy with FavID in order to extend remission. “This represents a significant departure from what we have seen in the past, and that departure is a consequence of the fact that the standard of care for lymphoma therapy has changed since the launch of Rituxan in 1997. Currently more than 90% of patients diagnosed with NHL will receive Rituxan to treat their disease,” said Dr. Longenecker.

While other studies with investigative immunotherapy products for NHL enrolled only treatment-naïve patients induced into remission with chemotherapy, Favrilie’s strategy was to deliver their active immunotherapy following a Rituxan-induced remission.

This approach allowed Favrilie to enroll patients in their clinical trials more quickly (18 months) than other agents in development (42 months in one instance). Dr. Longenecker said, “We believe the rapid enrollment in our clinical trials is reflective of what the market wants, which is Rituxan upfront, followed by FavID, which are two biologic agents with very little adverse events. This approach avoids the use of chemotherapy and has significant quality of life benefits.” [cont. on pg 32 >>](#)

This approach avoids the use of chemotherapy...



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Furthermore, Favrilie's clinical strategy has been to open up their trials to treat as many patients as possible, including treatment-naïve and refractory patients. In the initial open-label trial of FavID, only treatment-refractory patients were enrolled, which was reflective of Rituxan's labeled indication at that time for patients who had relapsed. Over time, however, the use of Rituxan expanded to front-line therapy. At the same time, Favrilie's Phase 2 program matured, and according to Dr. Longenecker, the company received a lot of requests from physicians and patient groups to open up their trials to newly-diagnosed patients. Favrilie responded, and as a result, patient enrollment surged.

"When we initiated our Phase 3 studies, we opened enrollment to both treatment-naïve and relapsed patients; however, newly-diagnosed patients flocked to our clinical trial program," said Dr. Longenecker. "From our point of view, and particularly from a business point of view, where we really want to capture patients in this treatment scheme is in the upfront setting, that is the newly diagnosed, treatment-naïve patient whose first-line of therapy would be Rituxan to induce remission, followed by FavID to increase the durability of disease remission," said Dr. Longenecker.

Further, he explained that while Rituxan induces remission in a large percentage of patients, remission is not long-lasting—Rituxan remains active for a period of several months after the one-month course of treatment consisting of once-weekly IV infusions. In time, however, the disease remits, thus illustrating the currently unmet clinical need—low-grade follicular or B-cell NHL remains incurable. FavID is believed to

extend a patient's remission indefinitely, he said. Favrilie reports that one patient on drug remains in remission 4 years out, and the company intends to treat patients on study with the booster regimen for as long as they remain in remission.

On the other hand, Genitope's clinical strategy approach involves the administration of its product following a chemotherapy-induced remission. Clinical trials conducted to date have given patients a 6-month break between the end of chemotherapy treatment and the beginning of their immunization regimen with MyVax. Therefore, Genitope's longer manufacturing throughput time (~3.5-6.5 months) is expected to be clinically irrelevant.

Trials have also been conducted in aggressive NHL in which immunization was initiated following a 3-month rest. Dr. Denney reported that similar rates of immune response have been observed in both groups. The timing and recommended use for MyVax will be a function of its labeling and FDA-approved indication, coupled with how physicians feel it is best to use the product in their patients, noted Dr. Denney.

Genitope's clinical trial strategy closely maps to the one piloted at Stanford and the NCI. "We were aware of rituximab when we started our Phase 2 and 3 trials, as the very first patients who received rituximab were in trials run by Dr. Ronald Levy at Stanford who is also one of the founders of Biogen Idec," said Dr. Denney. Rituxan is currently jointly marketed by Biogen Idec and Genentech.

"Our concern with using Rituxan upfront is that you knock out functionally half a patient's

...the current standard of care for follicular lymphoma is chemotherapy plus Rituxan...

immune response with that agent,” said Dr. Denney. “There is an argument that we can still get a T-cell response, and the T-cell response can be protective; however, there is also data to indicate that a B-cell depleted immune system is far from normal. So we don’t know how vigorous or protective a T-cell response you can get,” he said. Therefore, he reported that Genitope’s approach was to follow the path that had been demonstrated to be the one most likely to lead to success and ultimately, to approval. In addition, using a chemotherapy-first approach reserves Rituxan, if needed later on. Once MyVax gets approved, additional trials may examine other clinical strategies.

In addition, Dr. Denney noted that the current standard of care for follicular lymphoma is chemotherapy plus Rituxan, and Genitope is currently initiating a clinical trial of MyVax following that approach. “Certainly we are being very methodical and careful in our development approach. Our goal is to give physicians a series of well-designed trials that tell them how best to use this drug in their clinical practice,” he said.

Other Relevant Differences

Dr. Longenecker points to Faville’s investigational treatment regimen—FavID is initiated 2 months after Rituxan—and the 8-week manufacturing throughput as key differentiating aspects of their NHL product, noting that a barrier to KLH active immunotherapy development in the past has been cost-of-goods sold (COGS), which represents what it costs a company to manufacture a product.

“The fact that we can manufacture and begin to deliver our product in 8 weeks makes us very unique in this therapeutic arena,” he said.

“Other products in development for use after a chemotherapy-induced remission are initiated one year out, and only in patients who have maintained remission over that time.”

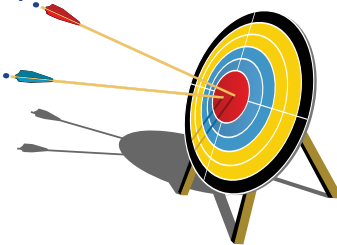
Dr. Longenecker believes, from a commercial point of view, that this is a difficult issue to resolve, as other companies will likely incur cost of goods without receiving revenue until their active immunotherapy is initiated one year out, and then only among patients who have not relapsed.

Data indicate that approximately 40% of patients would have relapsed over that time period, which Dr. Longenecker also believes can have an impact on COGS. Faville believes that the insect cell line process utilized during their manufacturing process may confer an immunogenic advantage to their active immunotherapy candidate.

Similar to the technology employed by the NCI, which is also studying an idotype vaccine for f-NHL, Genitope’s core gene amplification technology uses a mammalian cell line, the reasons for which stem from the early days of clinical development of an immunotherapy for NHL.

Dr. Denney said their choice of a mammalian cell production system was a conscious decision. One reason is that they wanted to stay close to the path piloted by Dr. Levy at Stanford and researchers at the NCI. Dr. Denney added that there is a concern, albeit we don’t know how large or inconsequential that concern may be, that the glycosylation involved in insect cell lines might alter the way in which a person’s immune system handles that protein.

Genitope decided that they did not want to potentially add another layer [cont. on pg 34 >>](#)





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of complexity onto their development process and therefore chose the more conservative approach of using mammalian cell lines. In addition, he said, the use of an insect cell line can be problematic in patients whose protein is produced at a low level, which could add appreciably to production failures in that type of system. Once Genitope's product is approved, Dr. Denney said it is possible that they could explore other protein-production methods in a careful and controlled manner.

Studies comparing insect cell and mammalian cell lines in this setting are expected to be announced this spring during the annual meeting of the American Association for Cancer Research (AACR).

Favrille utilizes a nanoparticulate formulation that allows FavID to be stable at refrigerated temperatures, which they anticipate will make the product easier to distribute and store. According to Dr. Longenecker, other active immunotherapies in development are most likely stored frozen, which could give Favrille a marketing advantage. These and other issues that stand to have an impact on transportation, on-site storage, administration, and reimbursement of the products could seriously affect the adoption and commercial success of either product candidate.

Next Steps for Immunotherapy for NHL and Beyond

Dr. Denney remarked that as Genitope continues to research and determine how to use active immunotherapy in patients with NHL, they anticipate that lessons learned may be applied to other types of cancers as well. Genitope recently expanded their research efforts to another B-cell cancer, chronic lymphocytic leukemia (CLL), where similar to their

efforts in NHL, the company is seeking ways to treat each person's cancer as a unique disease.

Considering the success of Rituxan in this patient population, Genitope feels that a personalized, active immunotherapy product has the potential to be a blockbuster product.

"A huge amount of money is spent to treat patients with NHL, and if you can bring a revolutionary drug to this marketplace, that's the definition of a blockbuster. We look forward to getting the results of our Phase 3 trials and getting this drug to market," remarked Dr. Denney.

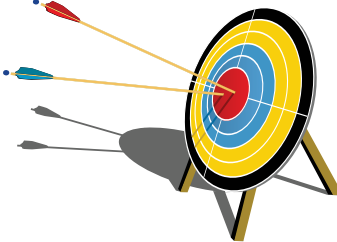
Delivering patient-specific therapies represents a fundamental shift in how cancer is treated. The next 2 years are expected to be crucial to the development, and commercial viability, of Genitope's and Favrille's NHL candidates, as well as for other types of active cancer immunotherapies in development.

Favrille's FavID is currently in Phase 3 development, and pivotal clinical trial data are expected to be announced in the 4th quarter of 2007. Genitope expects to release top-line results from their pivotal Phase 3 trial of MyVax by the end of this year, and a full reporting of the results at the American Society of Clinical Oncology (ASCO) spring of 2008 meeting.

A huge amount of money is spent to treat patients with NHL...

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The FDA issued a safety warning about heart and cancer risks arising from the overuse of a family of anemia treatments including Amgen's Aranesp® and Epogen® and J&J's Procrit®—two months before an FDA advisory meeting on May 10 to discuss potential problems. (*Wall Street Journal*, 3/10/07)



REIMBURSEMENT: Patient-specific cancer treatment is around the corner, but who will pay?

Personalized immunotherapies developed specifically for an individual patient carry the promise of revolutionizing the management of certain tumor types. But who will pay for these biologic therapies?

When asked that question, Joseph Bailes, MD, Co-Chair of Government Relations for the American Society of Clinical Oncology (ASCO) said, “It is important that the value cancer immunotherapy brings to patients be recognized in payment policies—both Medicare and private. Resources involved in developing and providing these therapies are likely to be different from currently available therapies, needing reimbursement rates and codes that reflect these treatments’ importance. This will help ensure cancer immunotherapy is integrated into the care of cancer.”

When Favrille, Genitope, and Dendreon were asked about reimbursement, all remarked that they do not anticipate significant third-party hurdles for their products.

One potential reason reimbursement may not represent a significant barrier to adoption is the overall cost of treating NHL. Dr. Denney of Genitope said that the lifetime costs of treating a person with NHL is estimated at \$1 million; therefore, any product that induced a long-term or lifelong remission would make financial sense.

Dr. Longenecker of Favrille said they anticipate offering a pricing structure that makes it easy for the provider and similar to the price-per-vial reimbursement methods already in place for other injectable/infused oncology products.

In addition, a model for personalized therapy has been somewhat established with a personalized cartilage product currently on the market with Carticel® [autologous cultured chondrocytes; Genzyme]. While

the model for cancer immunotherapy is somewhat different, a precedent for patient-specific therapy exists.

Still, the answer to a number of logistical questions regarding how these products will be reimbursed remains unknown. How will providers be reimbursed for the time and resources necessary to collect the blood or tissue sample (e.g., biopsy) that will be used to develop the personalized product? What about storage of the personalized product? If new freezers or storage facilities are necessary for multiple vials of personalized product for multiple patients, who will pay for that? How will providers be reimbursed for administration? What happens if a product is produced for a patient, but never delivered, or they are only able to receive a few doses, e.g., if the patient relapses or requires a change in treatment (recall the relapse rate for NHL is estimated to be as high as 40% in some treatment settings)? How then could the manufacturer re-coop their development cost?

Despite attempts to interview people in the reimbursement field about what they saw as possible challenges, many were unwilling to comment, perhaps because it is too soon. It is expected that once immunotherapy companies have final Phase 3 data in hand and products advance close to approval with the FDA, companies will conduct market research into reimbursement and begin negotiating with third-party payers, including managed care organizations and the Centers for Medicare and Medicaid Services (CMS). At least one company, Cell Genesys has stated publicly that they have already begun market research into reimbursement issues with a cancer immunotherapy product. As these products reach approval, discussion around reimbursement issues will likely increase and take a larger prominence in the conversation about product adoption. Stay tuned. **MNF**