THERAPEUTIC VACCINES
Portfolio Decisions for the Decade That Could Be

With the rapid recent growth of the vaccines market, approval of the first cancer vaccine, and multiple recent announcements in the area, Oliver Wyman examines the landscape of therapeutic vaccines, and asks how companies should consider adding a therapeutic vaccine to their portfolio, whether to pursue a more significant “critical mass,” or whether it is still too early for an investment in this therapy class.

The pharmaceutical industry has long recognized the potential of therapeutic vaccines—vaccines that treat a disease or condition by inducing or strengthening an immune response. But despite the existence of a handful of established therapeutic vaccines, most companies treated the category cautiously, as an idea whose time had not quite come.

That characterization may finally be changing. The past few years have seen a renewed focus on therapeutic vaccines. A key milestone was reached in 2010, when the FDA approved the first therapeutic vaccine for cancer. In the months since, companies have announced development milestones for an array of new therapeutic vaccines for other cancers, Alzheimer’s disease, and other conditions. The market for therapeutic vaccines is now projected to grow at approximately 55 percent per year, reaching ~$13 billion by 2018.

The space clearly offers opportunities for pharma companies to participate. Several hundred products are in development, many targeting conditions with high medical needs, some of which have eluded effective treatment for years. It is likely that multiple first-of-their-kind therapeutic vaccines will be introduced in the next decade, possibly including the first vaccines for breast and lung cancer. It is equally clear that it is feasible to access this pipeline, as demonstrated by a number of high-profile partnerships.

On the other hand, we have also seen the challenges faced by the first cancer therapeutic vaccine. Novelty is no guarantee of success, and a new category of products will have much to prove and many difficulties to overcome.

Given the state of and prospects for therapeutic vaccines, what is the right approach to take with therapeutic vaccines? How much should pharma companies invest in this potentially high-growth area? Is it too early (or too late) to make portfolio decisions on therapeutic vaccines?

Perhaps the key question is not whether to add therapeutic vaccines to the portfolio, but to what degree—is it best for an individual company to compete at scale, participate in spots, or remain uninvested? Historically, pharma companies with a focus in a therapeutic area have realized greater benefits than marginal players, with greater development success, greater access to new innovation, and higher revenues per product. Today, only one or two companies could be said to have achieved “critical mass” in therapeutic vaccines. Given the size of the development portfolio,

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1 Examples of existing therapeutic vaccines include those for rabies, hepatitis, and allergies.
the nature of the clinical benefits of these therapies, and the high number of unpartnered compounds, there is an opportunity for a company—or a few—to take the lead in therapeutic vaccines.

In this paper, we review the playing field and point to some key issues companies need to consider in determining whether they wish to pursue that leadership role.

THE THERAPEUTIC VACCINE PIPELINE

When we completed the research for this paper in late 2011, the pipeline for therapeutic vaccines had grown to an estimated 399 products\(^2\) and was larger than the pipeline for prophylactic vaccines.

The pipeline demonstrates some of the potential for this space: The vaccines in development cover more than 70 specific conditions. There is a strong focus on areas of high unmet need; for example, vaccines for cancer and infectious diseases (including HIV and hepatitis B and C) account for 55 percent and 24 percent of the pipeline respectively. Late-phase products are garnering particular attention. Products in Phase III include potential treatments for multiple cancers, allergies, diabetes, and addictions.

Therapeutic vaccines currently in development can potentially have a significant impact within the next decade. Many later-stage clinical trials are in place for immunotherapies for cancers of the prostate, breast, lung, and brain; for Alzheimer’s disease and for the treatment of chronic stress and the variety of conditions it causes. Products are also in development to treat multiple conditions with a single vaccine.

**IN DEVELOPMENT: 399 NEW THERAPEUTIC VACCINES**

<table>
<thead>
<tr>
<th>DEVELOPMENT BY PHASE(^\dagger)</th>
<th>CANCER</th>
<th>INFECTIOUS DISEASES</th>
<th>CHRONIC AND OTHER CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Clinical</td>
<td>149</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PRODUCTS IN DEVELOPMENT\(^\ddagger\)**

<table>
<thead>
<tr>
<th>TOTAL: 399</th>
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<tbody>
<tr>
<td>217</td>
</tr>
<tr>
<td>91</td>
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<tr>
<td>91</td>
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\(\dagger\) Count of products within therapeutic area
\(\ddagger\) Count by therapeutic area Q1, 2011

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\(^2\) Q1, 2011 Source: MedTRACK, Oliver Wyman Analysis

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Consider the range and scope of just a few of the developments announced in recent months:

- ImmunoCellular Therapeutics announced that it had been granted a patent for its dendritic cell-based vaccine targeting six tumor antigens involved in glioblastoma. The vaccine was in Phase II.
- Stemline Therapeutics presented data on a pair of Phase I/II trials of its stem-cell therapeutic vaccine SL-701. The results included two durable complete responses in glioblastoma and one patient with advanced glioma who experienced a 50 percent tumor shrinkage.
- Researchers from the Mayo Clinic and the University of Leeds published results of a trial in which 80 percent of mice treated with a vaccine made from DNA taken from healthy human prostates recovered from prostate cancer.

What could such a pipeline mean in the next decade? While therapy development always has uncertainties associated with it, the timeline above illustrates what the next decade of therapeutic vaccines could bring.

And this pipeline is still accessible to companies that wish to enter the space. While multinational companies have selectively increased their investments in the space, there are still significant opportunities for partnership.

- At the time of writing, about one in 10 therapeutic vaccines were being developed by major multinational firms (including GSK, Merck, Novartis, Sanofi, and Pfizer).
- In total, 15 organizations are developing 28 percent of the products in the pipeline, with the remaining 72 percent highly fragmented across 174 companies.

A number of high-profile partnerships have already been struck.

<table>
<thead>
<tr>
<th>Partnership</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galena Biopharma and Genentech for Neuvax E75</td>
<td>Galena Biopharma’s Neuvax E75 for breast cancer is a peptide-based TAA immunotherapy that recently successfully completed its Phase II trials. Galena announced in November 2011 an agreement with Genentech (a member of the Roche group) for clinical co-development of the product. Financial details of the agreement were not released.</td>
</tr>
<tr>
<td>Novartis and Transgene for TG4010</td>
<td>Transgene’s product is based on a recombinant vaccine virus expressing the MUC1 antigen and human Interleukin-2, targeting metastatic NSCLC. Transgene will conduct a Phase IIB/III trial of the therapeutic vaccine, and, upon completion of IIB, Novartis will have 90 days to exercise the option. If it does, Novartis takes on further development and commercialization costs, Transgene retains co-promotion rights for France and China, and Transgene is eligible for upfront and milestone payments of $10 and $950 million.</td>
</tr>
<tr>
<td>Pfizer and Cytos for Immunodrug Technology</td>
<td>Pfizer paid CHF 10 million upfront for the right to develop, in specified clinical areas, drugs based on Cytos’s Immunodrug technology—a VLP approach that permits targeting of both T and B cells. The deal includes milestone and technology transfer payments of up to CHF 140 million, plus research funding and royalty payments at a rate to be set according to sales volume.</td>
</tr>
</tbody>
</table>

Sources: Oliver Wyman Analysis, based on current pipeline and vaccine development benchmarks
But opportunities still remain.

**PARTNERED VS. UNPARTNERED: OPPORTUNITIES IN THE THERAPEUTIC VACCINE SPACE**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Partnered</th>
<th>Unpartnered</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>93 (23%)</td>
<td>306 (77%)</td>
<td>149</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td>140</td>
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<tr>
<td>Phase III</td>
<td></td>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

Sources: MedTRACK, Oliver Wyman Analysis

The scope of the pipeline, the accessibility of new candidates and technologies, and the ample opportunities for partnership all bring a sense of optimism to therapeutic vaccines. But that optimism should be tempered by the sobering results experienced by at least one recently approved therapeutic vaccine. Approval is only one hurdle to clear. In this case, payers have proven sensitive on pricing, fewer patients than predicted are eligible, physicians are concerned about the timing of reimbursement, and adoption has been disappointing. The result: once-exciting sales forecasts have been abandoned and the developers’ stock has fallen 85 percent below its peak.

**WHAT TO CONSIDER WHEN INVESTIGATING OPPORTUNITIES IN THERAPEUTIC VACCINES**

For a company to decide whether a set of therapeutic vaccine(s) may fit in their portfolio, there are several fundamental considerations to be addressed:

- **Fit with company strategy:** Will therapeutic vaccines be a synergistic advantage, a requirement to compete in a particular therapeutic area, or provide higher returns than what’s already in the portfolio? Do they represent an extension of what the company is already doing or an entirely new initiative?

- **Organizational fit:** Should a new therapeutic vaccine be integrated into an existing therapeutic area, placed in an existing vaccines division, or structured within a new business unit?

- **Commercial approach:** How different, if at all, should the commercial model be from the go-to-market approach used for other products? How well does such a model fit with the company’s existing capabilities?

The point of these questions is not that therapeutic vaccines are just like other therapies when it comes to investment considerations. For example, consider some of the unique questions a pharma company needs to weigh in making decisions on the commercial approach:

- Several products in development are personalized vaccines, using individuals’ cells to help trigger a desired immune response. Manufacturing requirements, production scale, and commercial implications differ significantly from mass-produced and delivered products.
  
  - Is your organization experienced with such a product?

- Payer perspectives may vary on their willingness to reimburse certain therapeutic vaccines, due to a combination of therapeutic vaccine price points, availability and price of substitute treatments, resulting impact of the vaccine, side effects, and other factors.
  
  - How would your organization’s Market Access and Pricing groups look to address such challenges?

- The regulatory pathways vary by country, and are highly nuanced for therapeutic vaccines.

  - Has your organization articulated a compelling regulatory strategy for the products?

And as the decision making moves beyond individual products and into the realm of portfolio, it is important to consider the company’s capabilities in the therapeutic area, in immunotherapies, and in certain other technology-related areas.
TO PLAY, OR NOT TO PLAY? FACTORS TO CONSIDER

- Which therapeutic vaccine capabilities – delivery, technology or production – need to be developed or obtained?
- Is the combination of internal TA capabilities and partner therapeutic vaccine knowledge sufficient for success?
- Is there an acquisition that provides both TA and therapeutic vaccine capabilities?
- What TA capability gaps – brand, commercial infrastructure, or other – need to be addressed to succeed in therapeutic vaccines? What is the plan to do this?
- Given the existing depth of capabilities, which partnering opportunities are most attractive?
- How does the organization ensure it captures the most value from combining its existing portfolio with therapeutic vaccines?
- Are therapeutic vaccines really the best option for the organization to pursue?
- What TA capability gaps – brand, commercial infrastructure, or other – need to be addressed to succeed in therapeutic vaccines? What is the plan to do this?

High
Low

TA CAPABILITIES
(R&D, commercial and other assets and experience within therapeutic vaccines target TAs)

Low
High

LEVEL OF IMMUNOTHERAPY CAPABILITIES
(Assets in specific platforms, technologies, or delivery mechanisms you could leverage, in addition to immunology experience)

Sources: Oliver Wyman Analysis

Technologically, therapeutic vaccine developers must choose among a variety of delivery mechanisms, product technologies, and production platforms—factors unique to therapeutic vaccines.

With an understanding of the pipeline and the partnering opportunities it offers, plus a perspective on how individual opportunities might fit the organization, companies are equipped to make investment decisions on therapeutic vaccines. But are one-off product decisions adequate? Should the focus instead be on small or large portfolios? Is there a whole greater than the sum of its parts?

Oliver Wyman’s recent review of R&D productivity, Beyond the Shadow of a Drought (November 2011), demonstrates the importance of concentration, or critical mass, in creating success in a therapeutic area. Our data demonstrate that companies which conduct more research (as measured by peer-reviewed publications), start more trials, and hold more products in their pipelines, see higher clinical success rates (phase transition success), more alliances (partnership agreements completed), and higher revenues per product.

DELIVERY MECHANISM

Developers are focused on exploring novel delivery devices as an opportunity to improve performance, increase ease of use for healthcare providers and/or patients, and reduce the cost of administration.

Select examples include:
- Nasal
- Sublingual
- Transdermal
- Electroporation

PRODUCT TECHNOLOGY

Manufacturers are exploring a variety of technologies to improve overall efficacy, timing and duration protection, as well as dosage requirements.

Select examples include:
- Natural or synthetic organisms used as vectors to express immunogenic proteins for HIV, various cancers, and malaria
- Virus-like particles used to explore vaccines for rheumatoid arthritis, allergies, and various cancers
- DNA vaccines express selected proteins, evoking immune responses for asthma, AIDS, and cancer

PRODUCTION PLATFORM

Many companies are attempting to develop and produce vaccines more quickly and more cost-effectively by investing in a concentrated set of production platforms that can be used across products.

Novel approaches are being explored, e.g.,
- Host cell lines
- Vector technology
- Media platform
- Production process technology and infrastructure.
In conducting this analysis, we looked at virtually all companies working in each of several therapeutic areas. We calculated average metrics for each therapeutic area. (For example, if a company had any diabetes assets in its pipeline, how many, on average, did it have? How many trials did it undertake on average?) We looked at companies significantly above and below the average, to see how well they did in successfully completing trials, publishing in peer-reviewed journals—and gaining revenue. The results were no surprise: A greater-than-average investment in a therapeutic area can pay benefits in development success, access to innovation, and ultimately in commercial success.

It is difficult to conduct a similar study for therapeutic vaccines. The whole field is much younger than categories such as diabetes or depression, and there are significantly fewer compounds, trials, and articles, to review. We can, however, look at metrics such as the number of products in pipeline, and when we do, it is clear that some companies are making greater investments in therapeutic vaccines. Merck and GlaxoSmithKline, for example, have several times as many products in their pipelines as some of their peers, and far more than the average therapeutic vaccine development company.

From the analysis above, we would expect Merck and GSK to do better than companies with significantly fewer therapeutic vaccine products in their pipelines. But from the magnitude of the total development pipeline and the low level of partnering to date, it is clear that there is still room for other players to join them. It will require commitment not just on the level of the individual product but on the organizational, therapeutic area, and broader immunotherapeutic levels, but we expect at least a few companies to partner and bring more of these promising new products into their portfolio, achieving critical mass and the benefits that go with it.

We look forward to watching the development of the therapeutic vaccine category over the coming decade. Will your company watch the developments—or participate with critical mass—in this space?
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