

Oncology shows highest potential in high-potency market

Are we approaching a decisive point in the war on cancer, or do newer targeted drugs represent a false dawn?

The market for high-potency (HiPo) ingredients has grown steadily since 2005. Of the different HiPo sectors, which offers the most opportunity for growth by 2010, and why?

There are many general criteria used to define the HiPo sector. For this discussion, we will view the HiPo market based on the therapeutic classes that have historically been labeled and controlled as HiPo substances: steroids, hormones, oncology drugs and others – a diverse set of therapeutic products, including cardiovascular drugs, central nervous system drugs, muscular-skeletal drugs, drugs for respiratory ailments, some anti-diabetic drugs, etc.

Of these four sectors, oncology accounts for more than half of the associated dosage market (Figure 1). The reason for this is a combination of several basic factors: No one has found a cure for cancer yet; people live longer, and therefore, are more likely to be affected by cancer; detection rates have improved; and survival rates have improved with the discovery and application of better drugs. These factors drive innovation – hence the greatly increased pharmaceutical research and development (R&D) activity in this field – but allied to this is an equally genuine need to control cost, which has spurred the huge demand for

generic oncology medicines.

More than 60% of all malignant cancer diagnoses in the US occur in people age 65 or older. There are an estimated 6.5 million adults age 65 or older currently living with a history of cancer in the US. That number will only go up as the country's baby boomer population ages and the number of men and women age 65 and older – currently about 36.8 million – doubles by the year 2030. Approximately 43% of these older men and women with cancer are expected to survive for 10 years or more and approximately 17% are expected to survive for 20 years or more after their initial diagnosis (1).

The other two large sectors of the HiPo dosage market, steroids and hormones, continue to grow, but that can be attributed to organic growth associated with the general increase in the global population and is not, as is the case with oncology, driven by an increased R&D focus. These steroidal and hormonal drugs are established products that effectively do the tasks ascribed to them. Therefore, there isn't a great need for a lot of research and development in these areas beyond modes of delivery and novel combinations of existing drugs.

This lack of R&D is in stark contrast to what's happening with oncology and the "other" category. This development is being fueled by an aging population that increasingly requires CNS and neurological medicines, many of which are highly potent. While compound annual growth rate is similar for oncology and "others", the oncology market is approximately four times the size of the "others" sector.

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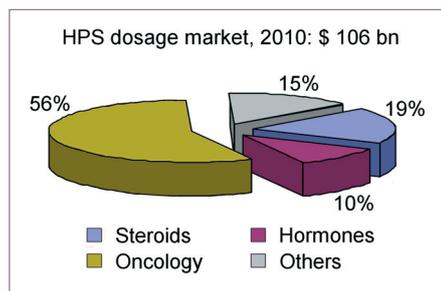


Figure 1

ONCOLOGY TRENDS

There is a significant amount of research

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and development spending happening in the oncology sector now, mainly in the US, but also strongly in Europe. The industry is specifically looking at novel therapeutic agents for use in the fight against cancer. The most significant change driving this interest is the shift in focus of the biotechnology industry, which is moving away from the traditional cytotoxic breakthroughs that occurred during the 1980s and 1990s.

Until the turn of this century, the majority of oncologic treatment was based on surgery, radiation therapy and the application of cytotoxic drugs and hormone antagonists – e.g., selective estrogen receptor modulators (SERM) and aromatase inhibitors (AI). In general, the treatment for primary and metastatic disease cancers focused on the eradication of cancer cells by treatments designed to kill off the cancerous cells with targeted radiation therapy or direct toxic effects of cytotoxic agents. Within the past 10 years, there has been a big swing in the type of cancer agents approved by the FDA (Table I).

There are two clear and significant trends: the decline in approval of both cytotoxic and hormonal antagonists and the rapid adoption of both monoclonal antibodies (MAbs) and small molecule targeted agents – often referred to as “cytostatics”. MAbs possess selectivity for particular cell surface antigens and exert their effects by either blocking cell signaling – as is the case with Herceptin – or recruiting the immune system via mechanisms such as Antibody Dependent Cell-mediated Cytotoxicity (ADCC).

Small molecule targeted agents exert their effects by inhibiting either intracellular kinases or extracellular growth factors (VEGF, EGFR). These key enzymes and growth stimulator factors are often up-regulated in cancer. Researchers are trending towards development of multi-targeted inhibitors of these kinases to improve their potency, duration of response and utility across different cancers. In some cases this can also lead to a greater potency and potential for side effects.

Allied to this is the prevalence of targeted small molecule therapies available in oral forms. This form has a number of advantages, including control of costs, patient preference and compliance. However, there are also greater manufacturing challenges. In almost all cases, the bioavailability of an oral medication is lower than one administered intravenously or as an injection. This presents two key challenges: higher volumes of APIs are required in a containment setting – lower bioavailability equates to more API per dose – and greater control of particle

size distribution (PSD) is necessary. The PSD of orally available medicines needs to be tightly controlled during manufacturing to ensure a reproducible effect each time the medicine is taken. For API producers, this means controlling particle size distribution within a pre-specified range to achieve the desired bioavailability and pharmacokinetic profile. Sometimes this is achievable by careful control of processing conditions, but we are seeing an increasing preference for suppliers with milling and sieving technologies and know-how.

This is not the only area of rapid growth in oncology. Another targeted approach is the area of clinical research into antibody drug conjugates (ADCs), which combine the targeting power of an antibody with the cell-killing power of ultra-potent cytotoxins, e.g. maytansinoids and aurastatins. Only one ADC (Mylotarg by Wyeth) has been launched, but this sector is set for rapid expansion due to the marked clinical efficacy demonstrated by high profile, late-phase candidates, e.g. Herceptin-DM1 and SGN-35 (fast track granted).

The area of small molecule targeted cytostatic drugs is clearly the area with the most growth potential at this point in time. Ethical cytotoxic drugs are still a viable opportunity, but the research and development trends show a move away from this. Health care facilities and drug manufacturers and suppliers have moral, ethical and legal obligations to protect people who handle cytotoxic drugs by keeping exposure within justified health protective limits like the European Medicines Evaluation Agency's (EMA) threshold of therapeutic concern (TTC) for genotoxic impurities. Additionally, there are often significant costs associated with the administration of cytotoxic drugs. These are due to the necessity of hospitalizing patients who require intravenous dosing – sometimes for several hours – and in many cases, because customized dosing is required based on the state of a patient's immune system and critical organ functions. The biggest opportunity in cytotoxic drugs is the supply of generic versions. The reduced price of generic drugs helps, albeit only partially, to offset the cost of hospitalization for expense-pressured health services. This combined with recent and continuing loss of patent protection of blockbuster cytotoxics is fueling the very rapid growth in generic cytotoxics (greater than 20% CAGR).

Despite the rise of generics, there is continuing research into safer and more convenient oral doses of commonly used cytotoxic drugs. This research

Table I

| | 1996 - 2000 | 2001 - 2008 | Trend |
|---------------------|-------------|-------------|-------------|
| Cytotoxic | 12 | 9 | -25% |
| Small mol. targeted | 0 | 9 | +++ |
| MAbs | 3 | 6 | 100% |
| Hormones | 10 | 7 | -30% |
| Immunomodulators | 2 | 2 | - |
| Other | 9 | 7 | -22% |
| Adjuvants | 16 | 4 | -75% |
| Total | 52 | 44 | -15% |

represents the primary area of innovator opportunity for the cytotoxic class.

The need for new drugs with novel modes of action seems set to continue, as it's highly improbable that any single agent or class of agents will have broadly applicable potential to cure cancer. The more modest and realistic scenario is that cancer would move to a state of chronic disease management (like heart disease treatment) with a combination of early detection, genetic profiling of the disease and the application of more synergistic combination therapies.

CARBOGEN AMCIS' new Bavla, Ahmedabad, India facility – set to launch in January 2010 – will offer significant capacity across multiple manufacturing cells and broad technology capabilities. Included in the technology capabilities, the facility will provide milling, with several proven techniques to allow for control of particle size between 1 and 1,000 microns. In the context of HiPo manufacturing, this is a big challenge. Reducing particle size – making it finer and dustier – makes containment more difficult. It is a clear trend that pharmaceutical companies prefer to work with contract manufacturing organizations (CMOs) with the capability to mill HiPo products.

INNOVATORS & SERVICE PROVIDERS

The most productive way for pharmaceutical companies to expend efforts is to focus research into the basics of human biology. Within this realm, companies should focus even further on the field of cancer research that investigates how accumulated mutations at the genetic level lead to survival and proliferation advantages for tumor cells. These mutations and altered gene expression profiles provide attractive targets for rationally designed drugs against the specific protein kinases for which these genes encode.

An area often criticized by the FDA when reviewing the development and commercialization of cancer drugs is the lack of efficacy-indicating biomarkers. When a new cancer therapy is developed, it is crucial to understand

that any demonstrated efficacy is attributable to the drugs proposed mode of action on its target. Where this relationship cannot be established due to the lack of a specific biomarker, the process of benchmarking a drug's efficacy against the standard of care and applicability in different disease settings becomes difficult. This can often lead to additional basic research and costly clinical trials before approval can be granted. Failure of drugs in late clinical trials, due to a lack of basic understanding of a drug's mode of action, is a very expensive way to fail. Pharmaceutical industry officials estimate the total cost of each new drug discovery to be \$ 800 million, as detailed in the appropriately titled book, "The \$ 800 Million Pill: The Truth Behind the Cost of New Drugs" (2). When a drug progresses all the way to clinical trials before being deemed a failure, that investment is a huge loss for the entire industry and its customers – patients.

If there are good biomarkers and analytical tools available early on in preclinical testing, drug developers can effectively weed out those compounds that really don't have a chance of making it to a test-stage drug.

For drug developers, focusing on underlying biology and translational research is a more effective and productive use of resources than retaining all activities, including development and manufacturing, in house. CMOs are often technically well-placed and more economical in the provision of development and manufacturing services. This is particularly true in the case of HiPo specialists who can optimally deploy their resources and assets over a number of parallel development activities. This is in contrast to pharmaceutical developers that inevitably end up carrying fixed costs even when demand is low. Focused efforts and combined in-house production, with external options to maximize supply chain flexibility, better meet the needs of both patients and the pharmaceutical industry.

Competitive API manufacturers offer a diverse toolbox in terms of technology, most notably in separation sciences, solid state services and drug conjugation. These capabilities are combined with a depth of services that include basic process research and development, clinical supply, commercialization and late life-cycle management.

Very few global CMOs offer the necessary expertise, experience and specialized assets required to successfully develop and commercialize drug conjugates – within the highest levels of containment and stringent

microbiological control. Because we are knowledgeable of trends in the industry and have deep experience with a broad selection of customers, we continue to substantially invest in antibody drug conjugations.

API manufacturers can add value by working closely with clients to define "smart" manufacturing regulatory, containment and productivity processes. When there is early engagement in the development process, CARBOGEN AMCIS can advise on the most appropriate starting point for the registered process, as well as explore how to minimize the length of the HiPo sequence. The objective is to produce the most inherently safe (minimal HiPo) and most economic (minimal GMP and HiPo) process achievable.

It is not uncommon during the early development stages to encounter a lengthy synthetic sequence, in which the potency of the molecule comes in at a relatively early stage. This is expensive from a manufacturing perspective when compared to a sequence with a "late convergence" that produces a highly potent intermediate or API at the end of the sequence. This result requires less use of HiPo assets.

The primary reasons pharmaceutical companies choose CARBOGEN AMCIS are its commercial capabilities and commercial track record with highly potent products. It was this reasoning that reinforced our decision to build the new facility in India. To gain a competitive advantage, it is not enough to be excellent from preclinical through phase two. Clients, especially emerging pharmaceutical companies, increasingly want a partner with the necessary combination of skills and assets to support a product through the rigors of commercialization and continue as the primary commercial supplier. When it comes to commercial supply, life-cycle management is an increasingly important consideration, and CMO's who are able to offer robust, economic commercial supply will have a significant advantage. As will those who can also offer dual site sourcing as a way of reducing overall supply chain risk. These benefits form the corner stone of our HiPo strategy, the key to which is the state-of-the-art HiPo manufacturing facility at Bavla.

Another increasingly important point during the commercialization process is alignment with the "Quality by Design" ethos described in the guidance from the International Conference on Harmonization (ICH). While this contains broad process validation concepts that have been around for some time, it also provides a disciplined approach to successful commercialization of drug products, which can be applied to APIs.

CMOs that are well versed in these concepts are also those best placed to meet their clients' expectations.

GENERICS

The growth in generic drugs manufacturing is fueled as much by collective national health providers and health insurers, as it is by any other factor. The rising cost of health care is simply not sustainable; health care providers are looking to generic versions of drugs to control costs wherever possible. This is particularly true in the case of some oncology treatments, especially newer therapies, which can be prohibitively expensive. Certain courses of treatment involving cocktails of drugs can cost in excess of \$ 30,000 per patient.

The growth in the generic market is prompting more companies to produce them, but the high investment and know-how barriers deter many. The boundaries between late life-cycle management, authorized generics and third-party generic supply are becoming increasingly blurred. In fact, many large pharmaceutical companies now have subsidiary business units focused specifically on the supply of generics. It is an accepted fact that generic competition is essential for the pharmaceutical industry, and the prevalence of generics – especially where complex and high-value medicines are involved – is set to continue.

Through its strategic investment in Bavla, CARBOGEN AMCIS positioned itself to service innovator partners with product life-cycle management. The company also proactively explores opportunities to maximize and prolong value from its late lifecycle HiPo portfolios.

Pharmaceutical suppliers should continue to monitor industry needs in order to be prepared to respond to pharmaceutical company, and by extension, patient demand. It is our business to stay ahead of industry demand, and through experience and strategic investments, we're ready to support key areas of growth.

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