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Anticancer Drugs: No option but to outsource?

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Anticancer agents represent the most dynamic segment of the pharmaceutical industry as reflected by both projected sales growth as well as pace of new product development.

At the dosage form level, anticancer drugs account for global sales of around \$50 billion, roughly corresponding to 7% of total pharmaceutical demand, these sales being projected to grow during the coming five years at 12% per annum, twice the pace anticipated for the pharmaceutical market as a whole.

Also during that span, a continuous flow of anticancer NAS (New Active Substance) is expected to reach the market. Within this framework, the pace of new product introductions observed in the last six years, where an average of six anticancer drugs — roughly corresponding to 20% of NAS launched every year — reached the market (see Figure 1), is unlikely to slacken, reflecting the number of projects in late development.

The dynamic development of anticancer drugs stems from various factors, mainly:

1. An expanding patient pool, driven by:

- * Graying world population with as a corresponding higher incidence of cancer, a set of pathologies largely corresponding to a degenerative-age related family of diseases
- * Improving healthcare standards outside the developed world, bringing cancer treatment within the reach of wider patient cohorts in regions such as South America or Asia
- * Advances in diagnostic procedures as well as wider spread screening programs amongst the general population, enabling detection of cancer in its earlier stages, when treatment is still an option

2. Improved survival rates amongst treated patients which translates to opportunities for longer treatment cycles

3. Introduction of new and more expensive anticancer drugs — the pace of new product launches expected to continue unabated, driven by the major unmet needs of the anticancer space, as demonstrated by the low survival rates observed for some types of cancers, like pancreas or liver.

Compared to other therapeutic segments, anticancer agents are characterized by distinctive traits. These include:

1. A peculiar product slate consisting of around 120 active substances, with the top 15 accounting for more than 70% of total sales. Important to note, this product slate covers both small molecules obtained through synthesis and hemisynthesis, the latter starting from a precursor obtained through extraction or fermentation, as well as large molecules (often referred to as biopharmaceuticals), chiefly monoclonal antibodies (MAbs), a product group that has enjoyed spectacular growth over the last five years, seeing its share of total anticancer sales jump from 15% in 2002 to 65% at present. It is interesting to note that the sales concentration dramatically differs between large and small molecule anticancer drugs, as reflected in the share of sales originating from the top three products: 80% for large molecules and 30% for small molecules.

2. Higher failure rates combined with shorter development cycles (see Figure 2) reflect both

- * the complex and often poorly understood mechanisms of cancer, resulting in investigation of products with new modes of action and greater development risks, exacerbated by the lack of clear clinical endpoints, and

- * a reduced development timeline, as fast-track status is often granted by the authorities like the FDA to get drugs onto the market as quickly as possible, leading to development times of just 57 months for some anticancer drugs, compared to 74 months in most other therapeutic segments.

3. Low volumes – most anticancer drugs have drug substance requirements well below the ton threshold, because of extremely high potency levels with a correspondingly low daily dosage, short treatment cycles, and an overall small treated patient pool compared to GP (General Practitioner) type of drugs like cardiovascular or CNS drugs.

4. Injectable formulations account for 80% of sales, with only a handful of anticancer drugs available as orals. This is due to such factors as stability and solubility issues, better control of dosages delivered to the patient, ease of handling considering also the typical multidrug regimens applied in cancer therapy, and the large share of biopharmaceuticals, for which injections continue to represent the sole practical delivery route.

Another important trait of anticancers is associated with the extreme toxicity and high biological activity intrinsic to several anticancers. This is particularly the case for traditional cytotoxics acting at various levels of the cell division and multiplication process, including, in addition to antimetabolic antibiotics such as doxorubicin:

1. Alkylating agents that bond covalently to the cellular DNA to inhibit its replication
2. Antimetabolites that interfere with the synthesis of amino and nucleic acids
3. Microtubule inhibitors like the various taxanes and vinca alkaloids, and
4. Topo-isomerase inhibitors that disrupt the unwinding of the DNA and prevent its replication.

Even though the trend is towards the development of more selective anticancer drugs with targeted mechanisms of action, especially biopharmaceuticals such as MAbs, small molecule-based therapies will undoubtedly continue to represent the backbone of anticancer treatment. Some exciting developments will also be associated with conjugates consisting of MAbs linked to highly active toxins, having potency levels an order of magnitude higher than traditional cytotoxics.

Such approaches may manage to combine the activity of cytotoxics with the selectivity typical of biomolecules and cell messengers, potentially providing “silver bullets” to the cancer anticancer arsenal.

At the 2013 horizon, small molecule-based anticancers are still expected to account for 55% of anticancer sales (see Figure 3). At the same time, the number of anticancer APIs is likely to continue to expand, while bulk requirements associated with any given product will remain low. They may even decrease, the same way that more focused targeted therapeutic protocols, tailored to the specific requirements of particular patient groups, address smaller target cohorts.

For pharmaceutical companies engaged in the anticancer space, these traits have major implications at all levels of the value chain. This is particularly the case in terms of supply chain management, both for the drug substance and drug product, challenges intrinsic to pharmaceutical manufacturing operations, including substantial fixed cost base, capital efficiency, asset obsolescence and regulatory compliance.

Pharmaceutical companies active in oncology simultaneously have to address a number of often apparently irreconcilable requirements, seeking a subtle equilibrium amongst these. For example:

Capital efficiency and capex mitigation considerations need to be balanced with investments associated with regulatory and safety standards intrinsic to the handling of highly potent substances. Within this framework, capex outlays for anticancer products are an order of magnitude higher compared to “normal potency” drugs. This is due to the high containment setup as well as massive infrastructure involved for anticancer drugs. At the same time the low volumes associated with most anticancer products must be taken into account. These often result in sky-high capex outlays expressed per unit of expected output, dwarfing averages noted in the pharmaceutical industry for “banal” products. The problem is further compounded by the massive infrastructure requirements — such as airlocks, high efficiency air filtration — that ideally should be shared across different production suites – a situation often clashing with the narrow anticancer lines typical of companies active in this segment.

Capex outlays must be carefully compared to risks of asset obsolescence relating to project attrition. This is the nightmare situation for every CFO, who faces the risk of allocating scarcer financial resources to build capacity for a molecule that may never reach the market. In addition to the substantial capex associated with anticancer drug manufacturing capacity, it is worth underlining that these types of assets are rarely suitable for producing other types of products, further compounding risks of capital and asset obsolescence. Similarly, training requirements cannot be underestimated; the safe handling of anticancer drugs involves a highly specialized workforce.

Long lead times associated with building and validating high containment facilities must be carefully balanced with the typically shorter development cycles observed with anticancers. This stresses the need to optimally calibrate the timing of investment considerations in order to be ready to supply the market as soon as the NDA is granted, while avoiding investing too early when attrition risks are still substantial.

Last but not least, the financial constraints typical of most emerging pharmaceutical companies — the main driver of innovation in anticancer development, with more than 70% of anticancer R&D projects stemming from this group of players (see Figure 4) — needs to be duly taken into account. Most emerging pharmaceutical companies have limited experience in manufacturing operations and also often have limited financial resources, stressing the imperative to carefully allocate these for optimal impact.

Against this background a possible alternative worth exploring is represented by outsourcing production to reliable specialized vendors, both for the drug product and the drug substance. API/drug substance vendors include such companies as Ampac, **Ash Stevens**, Helsinn, Novasep and Lonza, while formulated products providers include BSP, Ben Venue, Catalent, NextPharma and Patheon.

These companies have a long experience in handling high potency products including anticancers, having extensively invested in both production capacity and a trained workforce. In several cases relying on such vendors can represent an attractive alternative to investing in own

capacity, from a financial perspective as well as in terms of strategic risk mitigation and time-to-market issues.

Particular attention needs to be devoted to the selection of the outsourcing partners, as few industry suppliers offering formulation and finishing services have installed in their facilities state-of-the-art technology specially designed for optimal containment.

Through a third party vendor, a company engaged in anticancer drugs can almost instantly access the required capacity and skill base without committing upfront massive investments. The third party has better opportunities to effectively load and hence to achieve acceptable returns on the capital committed, sharing its risks on a broader basis.

Similarly, total-cost-of-ownership will often favor outsourcing. It is important for prospective customers to go beyond simply comparing the unit price paid to the vendor with variable costs that would be incurred should the product be manufactured in-house. Rather, the comparative analysis should take into account fully loaded costs including non-cash items such as depreciation as well as a risk premium reflecting the cost of capital.

In most cases, despite the mark-up applied over own costs incurred by the third party vendor, such an analysis will clearly favor the outsourcing options in terms of economics. Similarly, it is not necessarily true that outsourcing means foregoing the tax optimization opportunities often leveraged through in-house manufacturing activities. To this end, constructs such as long-term leasing or assumption of part of the investments by the customer in its own books often provide adequate degrees of freedom to play with transfer prices.

Does this mean that all pharmaceutical companies engaged in anticancer drugs should blindly rush towards outsourcing?

Not necessarily; the appropriateness of such a move hinges on a number of considerations, including the breadth of the anticancer portfolio as well as capacities on hand by the particular company. Similarly, selecting and relying on a third party vendor should not be viewed as an easy endeavor to be taken lightly – keys for success being represented by the ability of the customer to engage in an open dialogue with the vendor that has the required capabilities and skills.

To this end, a prerequisite is for the customer to allocate enough time upfront in performing appropriate due diligence on more than just the vendor's capacities.

As recognized by a famous Chinese general almost four millennia ago, ultimate success hinges on knowing not only the partner but also ourselves!

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