Plants as Factories – A Manufacturing Solution for the Biopharmaceutical Industry?

Plant molecular farming or ‘biopharming’ has the potential to overcome shortcomings in pharmaceutical manufacturing – provided issues such as public perceptions and regulatory concerns can be resolved.

By Phil Webster at Frost & Sullivan

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One of the biggest barriers to the biopharmaceutical industry is the cost of product manufacture. Large-scale manufacturing facilities are expensive to set up and scaling up manufacture to a large capacity system is a time-consuming and costly process. Downstream processing methodologies are complicated and inefficient, and there are inherent safety concerns regarding potential microbial contamination of a conventional fermentation vessel. For these reasons, therefore, there is demand for an innovative manufacturing system to fuel the rapidly expanding $45,000 million biopharmaceutical market.

Plant molecular farming or ‘biopharming’ involves the use of transgenic plants which are engineered to express therapeutic proteins. The plants are essentially used as factories, and as such have significant potential to remove this bottleneck in pharmaceutical manufacturing and drive expansion of the biopharmaceutical industry forwards.

KEY ADVANTAGES OF BIOPHARMING

The biggest advantage of biopharming is its potential to reduce biopharmaceutical manufacturing costs. The primary cost saving is made through the increased yield of plants compared with microbial systems. Secondary savings can be made through the use of existing agricultural practices and machinery to harvest the transgenic crops, and scalability is also improved by simply growing a larger area of crop according to demand.

The bioprocessing characteristics of plant-derived products are more straightforward, and there is a lower risk of contamination compared with existing systems, where microbial contamination can pose a potential health risk when dealing with biological products. The expression of novel proteins can be targeted to a specific plant tissue – facilitating simple harvesting, and safe and consistent expression.

Biopharming has the greatest potential in areas where biopharmaceutical products are required in large, reproducible volumes. The sector which is receiving the most research interest currently is that of monoclonal antibodies, which can be mass-produced in plants and used where a highly specific treatment is required. Research has taken place into treatments for areas of unmet medical need – such as diabetes, cancer and Alzheimer’s disease. However, no therapeutic products manufactured in plants have yet reached the market.

A second major sector for biopharming is that of the manufacture of low-cost industrial enzymes, used at a non-therapeutic grade for the secondary manufacture of therapeutic products. Products such as trypsin and aprotinin manufactured from agricultural crop plants are already in commercial-scale production.

BIOPHARMING MARKET ANALYSIS

Transgenic crops have been commercially available for almost 10 years, and the market consists of two main sectors – crops conferring herbicide tolerance and those conferring insect resistance. The US is the biggest grower of transgenic crops, with 42 million hectares grown in 2003, making up 63% of the entire sector and generating revenues of $1,500 million annually.

However, the market for biopharmed products is still at the emerging stage, and to date three products manufactured in transgenic plants have been commercialised for use as industrial enzymes. Prodigene Inc (College Station, Texas) manufactures trypsin (TrypZean) and aprotinin
agricultural biotechnology companies such as Dow Plant Pharmaceuticals (Indianapolis, Indiana) and Syngenta, which already have established reputations in the agricultural biotechnology market.

The least developed third tier comprises the product developers themselves, as this is a relatively untried sector with no established products and is therefore the most risky for industry participants. Within this sector, the first products for therapeutic use are approaching the final stages of clinical trials. The closest product to market is CaroRx for the treatment of dental caries, which is manufactured by Planet Biotechnology Inc (Hayward, California) and is in Phase III clinical trials. Planet specialises in the expression of secretory Ig A antibodies in tobacco plants, which are more resistant to proteolytic degradation than conventional Ig G variants, and can be expressed at higher levels. Planet is collaborating with LSBC concerning the extraction of the CaroRx product, which could potentially reach the market in 2006. The company also has two other early stage products in clinical trials: RhinoRx for the treatment of the common cold, and DoxoRx for the treatment of chemotherapy-induced alopecia.

North America (comprising the US and Canada) is predicted to be the biggest consumer for biopharmed products, predominantly because it is currently the biggest consumer of biopharmaceuticals. The market forecast for the total market for biopharmed products for therapeutic use is shown in Figure 1. No therapeutics are anticipated for launch before 2006, but the revenues generated from these products have the potential to drive the market to an estimated $2,200 million by 2011, at a rate of 104.3% – with this high growth rate indicating that the market is effectively starting from zero. Market expansion will be highest around 2007-2008 as revenues from products released early in the development phase are realised. From 2011 onwards, the market is expected to continue expanding as drugs released late in the forecast period generate further revenues, and new products enter the development pipeline. The anticipated adoption rate of new products is likely to be fuelled by the relatively lower cost of products manufactured from biopharming compared with conventionally manufactured biopharmaceuticals.

The market in Europe is expected to follow similar trends, but at a slower rate owing to the unofficial moratorium on growing transgenic crops for commercial purposes. However, this moratorium is showing signs of weakening, with Bulgaria, Romania, Spain and Germany now undertaking field trials, and market approval granted in May 2004 for a pest-resistant sweetcorn manufactured by Syngenta AG (Basel, Switzerland) – the first transgenic food product to be approved since 1998. The rate of European expansion is expected to be further hindered by the slow pace of definitive legislation across different member countries.

COMPETITIVE ANALYSIS AND PRODUCT PIPELINES

Competitors within the market comprise three tiers, as illustrated in Figure 2. The first tier consists of technology providers; these focus on the genetic engineering and tissue culture systems which are required to manufacture plants capable of expressing novel proteins. These industry participants are at an advanced stage in the wake of the agricultural biotechnology revolution.

In the second tier, there are industry participants offering full-scale production platforms and services to third parties wishing to manufacture a new biopharmaceutical product. These predominantly consist of large

agricultural biotechnology companies such as Dow Plant Pharmaceuticals (Indianapolis, Indiana) and Syngenta, which already have established reputations in the agricultural biotechnology market.

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LSBC is the largest specialist in the biopharming industry, and maintains the first commercial-scale growing facility – a 27,000sq.ft greenhouse system. In addition to providing manufacturing facilities for a range of clients including Prodigene, LSBC is developing its own portfolio of monoclonal antibodies produced in tobacco plants for the treatment of diseases of unmet medical need, including Non-Hodgkins Lymphoma and Fabry's Disease; these are in Phase I clinical trials.

In Europe, Meristem Therapeutics SA (Clermont-Ferrand, France) is closest to market with a form of gastric lipase for the treatment of cystic fibrosis. The product, which is expressed in corn plants, is entering Phase IIB clinical trials and could potentially reach the market in 2007. Cobento Biotech A/S (Aarhus, Denmark) also has human recombinant intrinsic factor in Phase II trials; this can be used as a dietary supplement for the treatment of vitamin B12 deficiency.

REGULATORY AND SAFETY ISSUES POSE A CHALLENGE TO THE INDUSTRY

The biggest challenge in plant molecular farming is the longstanding negative public perception of transgenic crops. There is a preconception that food safety may be compromised and that transgenic crops may have an adverse effect on human health. From an environmental perspective, concerns over non-target impacts of transgenic crops – as well as gene transgression to other plants and unrelated species – may have an undesirable impact. Thus far, no scientific evidence has been published indicating that currently commercialised transgenic crops have a negative effect, but further scientific investigation is required on a case-by-case basis.

A second major challenge is from a regulatory perspective. In this new and emerging area, no international guidelines are currently available. Transgenic crops have been strongly opposed by some countries, with an unofficial moratorium in Europe. However, this perception is expected to change, as exhibited by the recent decision of Spain and Germany to resume small-scale transgenic crop field trials and production.

The challenge of introducing any novel manufacturing practice to an established industry is difficult, particularly when faced with regulatory and safety concerns. This in turn is having an effect on the amount of funding being made available from venture capital firms, which are reluctant to invest in sectors which are slow in showing significant returns. The biopharming industry consists overwhelmingly of start-up companies which are still at the venture capital stage, and this is having a significant impact on further market development, with only one company (Chlorogen Inc) emerging into the market in the last three years.

TECHNOLOGY INNOVATION POISED TO OVERCOME INDUSTRY CHALLENGES

These industry challenges can be overcome with the implementation and development of innovative technologies, and several industry participants are moving in this direction. Two companies are leading the way in overcoming environmental containment and safety issues. Biolex Inc (Pittsboro, North Carolina) uses recombinant lemna – a small green aquatic plant with a rapid growth rate and turnover – grown in transparent bioreactors to produce a high yield of recombinant proteins. Greenovation GmbH (Freiberg, Germany) uses a similar system using moss within an enclosed bioreactor system.

Chlorogen Inc (St Louis, Missouri) is working on the expression of therapeutic proteins in the chloroplasts of transgenic tobacco plants. Chloroplasts are the light absorbing structures found in plant cells which give them their green colour; their DNA is not transferred to other plants, making them the ideal structures for the expression of novel proteins.

Technologies such as these not only eliminate potential safety and environmental concerns, but also have a significant impact on improving public acceptability of biopharming. This would encourage consumers to invest in the products, and would draw investment from major biopharmaceutical manufacturers interested in technology licensing and the outsourcing of manufacturing processes.

CONCLUSION

Plant molecular farming has the potential to become a major new method for the low-cost mass production of biopharmaceuticals. However, a poorly defined regulatory system and potentially unfavourable public perception are having an impact on the amount of funding being made available for the sector. The industry as a whole is focusing on these challenges, and the use of innovative technologies to overcome public and regulatory concerns will see this market develop to maturity.

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