PRODUCTION OF BIOPHARMACEUTICALS IN CORN: ISSUES IN SUPPLY CHAIN DEVELOPMENT; FROM R&D TO FULL SCALE MANUFACTURING

Scott E. Keeler
Plant-Based Biopharmaceuticals, The Dow Chemical Company

Abstract:

With eleven products presently on the market, representing greater than $2 billion per year in sales, and representing approximately 20% of new drugs in the development pipeline, the production of monoclonal antibodies (MAbs) for use as human therapeutics is an area that is presently receiving a great deal of attention. Transgenic plant-based production has the potential to be significantly more cost effective than the current cell culture approach for the production of large volume products (in excess of one metric tonne per annum).

However, the use of plants (e.g. corn) to produce biopharmaceuticals for human use, generates significant uncertainties and trade-offs involving a number of important process and product development issues in a manner not generally addressed as part of the development of a robust supply chain. These issues generally fall into four categories:

- dynamic political and public perception (especially with respect to both short term and long term regulatory requirements)
- field containment of DNA and protein
- uncontrollable factors affecting biological variability
- lengthy development timelines (biological, process, construction)

The production of biopharmaceuticals in plants is a regulated industry where approval must be sought each year (from initial development through the life of the product) for permission to grow the crop that produces the product of interest. Given recent events like StarLink, and the active movements in various parts of the world against the generation of genetically modified plants and foodstuffs, the regulatory landscape is highly variable and has the potential to be significantly altered over the course of the lifetime of any given product. One of the numerous places this debate impacts supply chain development is the stringency of the requirements for field production of crops. Is containment of the protein adequate, or is containment of DNA required? How does one develop a cost-effective supply chain for the production of large amounts of protein while taking into account the impact of uncertain Environment, Health and Safety (EH&S) requirements along with the vagaries of climate, location, pestilence, activists and other uncontrollable factors?

Typically, it takes four months to produce one generation of corn. Because of this fact, it can take as long as 18 months from receipt of the gene of interest until the first small amounts of protein are produced. Approximately two years after project initiation enough protein exists to begin serious process development, formulation and toxicology studies, and to initiate initial Phase I human clinical trials. However, because of the speed with which corn can be bulked-up from generation to generation, within another year the potential exists to have enough material to initiate the pivotal Phase III human clinical trials, with product launch as early as one year later. In the interim a fully optimized production facility must be designed, built and validated to meet FDA cGMP requirements (after which further process improvements are costly and time-consuming) in order to supply material for product launch.

This talk will attempt to frame some of these issues with a ‘real world’ example.