

IN brief

Europe plans for drug-making plants

In August, the European Food Safety Authority (EFSA) published its first guidelines for growing genetically modified (GM) plants for purposes other than food, such as producing drugs, industrial enzymes, raw materials for biofuels and phytoremediation. As these types of GM plants contain bioactive substances, the guidance addresses the possibility of accidental ingestion by humans, animals or wildlife. Applicants who intend to grow them commercially must submit a risk dossier to Parma, Italy-based EFSA, as well as a description of how they would confine plants under every conceivable condition, so errant genes cannot mix with other plants or escape through sewage or drainage. "We found that existing guidance documents for food and feed users were excellent ones," says Joachim Schiemann, former member of an EFSA panel on GM organisms. "The guidelines are generic, but there is a step-by-step analysis and case-by-case approach depending on the objective of the crop," said Agnes Ricroch, researcher at the University of Orsay in Paris. Ricroch praised the guidelines for considering the risk of exposure to humans, animals and other plants. "It asks the applicant to imagine the worst case," says Ricroch. "It is very important, because the companies should think about a Plan B."

Wendy Wolfson

Pfizer lured to Sweden

Pfizer has inaugurated a newly built 6,000 square meter, €150 (\$218) million biomanufacturing facility in Strangnäs, Sweden, next to an existing plant previously owned by Pharmacia (acquired by New York-based Pfizer in 2003). When fully operational in 2011, the facility will make acromegaly treatment Somavert (pegvisomant) and recombinant DNA growth hormone Genotropin (somatotropin), with the added flexibility to produce other biologics, possibly for contract. The new facility will be connected to the existing one, easing the flow of materials and personnel. "This is one of the largest investments in biomanufacturing in Scandinavia for a long time," comments Ylva Hultman Erlandsson, life sciences business development manager at Stockholm Business Region Development. Erlandsson, who was instrumental in securing the facility for Sweden, adds that Puerto Rico, Singapore and Ireland were strong contenders for the new plant's location. "The most important reason for Pfizer's decision to locate here is that there has been bioproduction in Sweden for a long time and there are unique competences and experience in the Stockholm region." Sweden has a strong track record in biologics manufacture—both Genotropin and Fragmin are of Swedish origin. Erlandsson also cites strong local and national support. "There was very good cooperation from everyone, including the Prime Minister and all the different agencies—all of whom really wanted Pfizer to establish this business in Sweden," she says

Susan Aldridge

Spotlight focuses on protein-misfolding therapies

A new drug candidate has, for the first time, modified disease progression in patients with a rare inherited protein-misfolding neuropathy. Initial results from pivotal phase 2/3 trials released by Cambridge, Massachusetts company FoldRx at the end of July suggest their compound tafamidis meglumine (FX-1006A) could be the first to successfully treat the genetic disorder transthyretin (TTR) amyloid polyneuropathy. The positive findings lend credence to the therapeutic targeting of misfolded protein to treat a raft of human diseases where insoluble protein aggregates known as amyloid are implicated.

The FoldRx trial is the first randomized, controlled trial ever completed in TTR amyloid polyneuropathy, a slow, progressive disease affecting up to 10,000 people worldwide. Pathogenesis is thought to be due to dissociation of a tetramer of the transport protein TTR, which leads to aggregation into toxic amyloid fibrils that subsequently accumulate in nerve, gut and heart tissue. The study enrolled 128 patients with the disease, who carried a confirmed V30M mutation—the most prevalent variant. Over the 18-month study, tafamidis halted disease progression, measured by the neuropathy impairment score, and quality of life—two endpoints which correlate with disease severity and serve as endpoints for neuropathy disease progression—while patients on placebo worsened.

Tafamidis, an oral, small-molecule chaperone, is a modified form of the non-steroidal agent diflusalin. The drug works by stabilizing the TTR protein complex into its normal tetrameric conformation, preventing its dissociation into the fibril-forming monomers. "This is the first drug that's ever done anything in these diseases," says Joel Buxbaum of the Scripps Institute in La Jolla, California, where the groundwork for the small-molecule tafamidis was performed. "This is clearly a molecule that is first in its class." Tafamidis may be unique among anti-amyloid agents because rather than target the fibrils, it acts by stabilizing the TTR tetramer, which reduces the availability of dissociated monomers, that are the fibril precursors. But Buxbaum points out that the therapeutic strategy is the same as for other protein-misfolding diseases, including those that do not involve amyloid. The aim is to reduce the amount of a misfolding precursor, whether by stabilization, in the case of TTR, or by inhibiting an enzyme.

"A wide range of protein-misfolding disorders are driven by the overproduction of mutant protein or in some cases, the overproduction of the protein itself," says John Maraganore, CEO of Alnylam Pharmaceuticals, also in Cambridge. Alnylam, for its part, expects to seek regulatory approval to begin human studies of an siRNA against TTR by the end of 2009, and also has an early-stage siRNA program in Parkinson's. "There are data with synuclein that [indicates that] triplication of the allele leads to pathology in the genetic causes of Parkinson's," he says, "so there are clearly both quantitative and qualitative changes in these proteins that make them pathogenic."

Using siRNA to downregulate the expression of a protein that might be important in a misfolding disorder "is a situation that is begging for a trial," according to John Berk, clinical director of the Amyloid Treatment and Research Program at Boston University School of Medicine, which is conducting a randomized, controlled trial of diflusalin in TTR. In TTR as well as other protein-misfolding diseases, the misfolded protein is probably there from day one, says Scripps' Buxbaum. "As soon as you turn on the gene, it's expressed," he says, and to that extent, all of these diseases are age dependent. "The phenomenon that goes on in transthyretin amyloid once you start to deal with the misfolded monomer, it's probably going on in all of these diseases."

Mark Ratner



Abnormal deposits of misfolded protein, shown in red, accumulate in body organs threatening healthy function. Prion diseases, diabetes, Parkinson's disease, Alzheimer's disease, Huntington's disease and transthyretin amyloidosis share misfolded protein deposits as a common feature.

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