

# Plant-made pharmaceuticals: Opportunities and safety

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One promising type of agricultural biotechnology generates plants that produce valuable biological substances, enabling agricultural crops to be used as “production systems” to supply these materials. Medical drugs, anti-bioterror vaccines, industrial enzymes, specialty plastics, and novel food ingredients can all be produced by this new application for plants, which is sometimes generically referred to as “plant molecular farming.” A particularly appealing aspect of this branch of plant biotechnology is its potential for simultaneous contributions to medicine/materials manufacturing and to the farm economy.

The fastest-moving application of plant molecular farming today is focused on the production of protein-type pharmaceuticals and vaccines, the demand for which is constantly increasing. Protein medicinals that are not normally found in plants, but rather are made using genetically engineered plants as the production system, are known as “plant-made pharmaceuticals” or PMPs.

## **Question: How are plant-made pharmaceuticals derived?**

**Answer:** To make a pharmaceutical protein, the plant that is to accumulate it in its leaves, seeds, etc, must first be genetically engineered to contain and express the gene which encodes that protein. Typically, the intended host plant would not normally contain this gene, which might occur naturally in a microorganism (such as a bacterium or fungus), another plant, or even an animal. Several different techniques have been developed for introduction of the appropriate gene into the host plant so that it will direct the plant to produce very large quantities of the protein product. The resulting transgenic plant making the PMP can then be grown either indoors or in the field, and the product extracted and purified from the harvested leaves, seeds etc.

## **Q: What sorts of pharmaceuticals can be made using plants?**

**A:** There have been many demonstrations of the PMP concept, using many different plants and a wide variety of protein products. The latter range from vaccines effective against malaria and other infectious diseases, to antibody-type proteins to treat medical conditions such as tooth decay and cancers, to enzymes that correct genetic-deficiency diseases. Even familiar blood constituents like hemoglobin have been made in transgenic plants. As long as the medical drug is a protein, and as long as it does not require certain additional, non-protein modifications in order to become medically active, it is fair to say that it can probably be made in plants.

**Q: What sort of plants, and plant materials, can be used for PMP production?**

**A:** In order to be economically viable, the PMP strategy requires the use of gene-expression technology that achieves very high accumulation of the protein product in the plant. There are only a few such technologies available, and each one tends to be specific to, or optimal with, just a few plant species.

Suitable plants for which such technologies exist include tobacco, corn (maize), rice, canola, safflower, alfalfa, and the small aquatic plant called *Lemna*. Depending on the particular gene-expression technology used, the PMP product can accumulate in the leaves (of plants such as tobacco and alfalfa), or in the seeds or fruits (corn and rice, for example).

**Q: What are the advantages of using plants, as opposed to other methods, to manufacture these medicinal proteins?**

**A:** Proteins are complex biological molecules, and although they may be produced by chemical synthesis in the future, their production today requires the use of a living system. The traditional, established method has used large-scale culturing (fermentation) of bacterial, fungal, or animal cells. The capability of these expensive fermentation systems to keep up with an increasing demand for greater diversity and larger amounts of protein pharmaceuticals is uncertain. Thus, approaches that are potentially more economical to set up have been suggested; this is one reason why PMP, which is actually quite an old and well-proven technology, is receiving considerable attention today.

However, claims that production of medical proteins in plants would be almost effortless and cheap should be viewed with some skepticism: while the cost of crop production in fields or greenhouses may be much less than the costs incurred in operating fermentation facilities, the subsequent cost of extracting and purifying the protein product from plants will vary considerably from protein to protein and between different plants. Thus, it is difficult to generalize regarding the overall economics of the PMP approach. Nevertheless, it seems likely that plants will offer some advantages relative to fermentation, especially in regard to flexibility and economy of scale-up.

**Q: How can farmers take advantage of the PMP opportunity?**

**A:** Because the PMP strategy uses customized (transgenic) plant varieties and addresses specialized markets, it does not make sense for growers to produce the crop speculatively. It seems much more likely that farmers will engage in contract production for PMP companies and/or pharmaceutical companies, with the contract partner supplying the seed and receiving the harvested plant material for subsequent processing.

To-date, such contracted production has been minimal and experimental, but in the future the range and quantities of proteins required may support substantial acreages of production.

**Q: How significant will PMP become as a new crop opportunity for farmers — can we expect small, ‘niche’ acreage or production on a very large scale?**

**A:** This is a frequently heard question, and the answer is that the agricultural prospect depends on the particular medical product being manufactured. Some products, such as anti-bioterror vaccines or drugs for commonly occurring diseases, may be required in very large quantities that will, in turn, require plant production on potentially many hundreds of planted acres per product. In contrast, the markets for medical drugs for rare disease conditions may be sufficiently small that greenhouse-scale production may suffice for them.

**Q: The possible use of food plants for PMP applications raises the question of whether transgenic plants could accidentally mix with their regular, non-PMP counterparts, resulting in the presence of the pharmaceuticals in food products. How likely is that scenario, and what can be done to safeguard against it?**

**A:** While some food crops (especially corn) are well suited for PMP production because they have been well characterized and they provide large storage capacity of proteins, some observers of the PMP approach to protein manufacturing have suggested that it should only be conducted with certain plants (such as tobacco and *Lemna*) that are not used as food for humans or feed for livestock. Several companies are also working to commercialize PMP opportunities with those plants. In the future it is likely that several plant systems will be used since different PMP gene-expression technologies and different plants are better suited for expression of some proteins than for others.

Depending on the PMP produced, there will be different needs for “containment” of PMP plants so as to avoid either genetic contamination (via pollination) or physical contamination (accidental mixing of seeds or harvested plant material) of the corresponding non-PMP crop. Containment options continue to be explored, including growing the plants indoors or in underground caverns (caves, mines), using sterile plants, maintaining strict separation distances from other plantings, or even growing in regions where the conventional, non-PMP crop is never produced.

Today’s largely experimental production of PMP plants is controlled by very stringent governmental regulation (including the U.S. Department of Agriculture). It is quite possible that strict controls will remain in place when PMP becomes routine and practiced on a larger scale.

### **References and further reading**

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<http://www.bio.org/healthcare/pmp>, Biotechnology Industry Organization (BIO) articles on plant-made pharmaceuticals.