

2025: global trends to improve human health - From basic food via functional food, pharma-food to pharma-farming and pharmaceuticals

Part 2: Pharma-food, pharma-farming and pharmaceuticals

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In a first part published in the November/december 2006 issue of *Agro-Food-Industry Hi-Tech*, global trends to improve human health were shown giving focus on food security, minimal basic nutrition, life style and eating habits, role of food in transition, transformation of the food industry, diversity of food, information about food, demographic shifts and aging populations.

In the second part focus is given on the transformation of health care, pharmaceuticals from plants, transformation of the production of pharmaceuticals, plant-made pharmaceuticals, plant bio-pharming, pharma-farming, transformation of crop production, nanobiotechnology and a Vision 2025.

TRANSFORMATION OF HEALTH CARE

Health and health care are in the midst of a transformation. Medicine is becoming more proactive, with its increasing knowledge of intrinsic genetic factors affecting disease risk and socio-economic, environmental and behavioural determinants of health. Lifestyle-related chronic diseases and the increasing costs of health care are other driving forces behind the search for creative, innovative and cost-effective ways to improve human health and prevent diseases.

An over-arching trend in health care is *'do it yourself'*. In the US, 73 percent prefer to self-treat, 80 percent have self-diagnosed when they visit a physician. Furthermore, healthy eating is better than medication - 80 percent purchase to avoid undesirable ingredients, 76 percent choose fortified foods. There is a crossover from failed dietary supplements to fortified, functional and medical foods.

Poor nutrition associated with weight loss is a strong predictor of increased mortality for the elderly. Very often micronutrient deficiencies have been associated with vascular diseases, cognitive decline and dementia in the elderly. Diets, that contain adequate levels of certain micronutrients, or micronutrient supplementation, may reduce the risk of developing such disorders. A good overview titled *"Diet, ageing and dementia"* is given by Muller in this journal May/June, 2006 (1). Aging-related diets are more and more relevant for improving health of old people. In China, since more than 4,000 years the Reishi Mushroom, *Ganoderma lucidum*, commonly referred to as Ling zhi, or "God's Herb" is used. This herb is known by the Taoists as the *'mushroom of immortality'* and has been considered to promote longevity. Reishi contains several constituents, including sterols, coumarin,

mannitol, polysaccharids, and triterpenoids called ganoderic acids. It is known to be an immune modulator and potent antioxidant and used to regulate blood pressure, to reduce cholesterol and blood lipid levels (2). For the record, the Reishi Mushroom is a food and not a pharmaceutical.

"Feed Your Genes Right - Eat to Turn off Disease-Causing Genes and Slow Down Aging" is a book written by Jack Challem in 2005 (3). It is a review of the nutrigenomics breakthrough describing reverse age-related DNA damage, prevention of inherited diseases, loss of weight and the way to feel better. Nutrigenomics is still a very young scientific discipline. Scientists use it as a way to find out how individual food ingredients or a defined number of food ingredients influence human metabolism on the basis of an individual genome. Key target is to develop personalized nutrition. Although nutritional science is still in its infancy, it will be possible in future to understand the complex interactions between individual nutritive ingredients and the genome, the transcriptome, the proteome and the metabolome (4,5). People will get their personal *'Chip Laboratory'* as a diagnostic or bioanalysis kit in order to go for a nutrition therapy which will improve their health. Personalized nutrition will be possible, and tailored foods will be offered, providing combinations of nutrients and bioactives with proven efficacy to mitigate diseases or prevent their onset. A similar trend is coming up in the area of medicine. Medicines are unique, but patients are very different. Nearly 30 percent of patients do not benefit from medicines. Significant numbers of patients suffer from negative side effects. Consequently, the health care system and health care business will be shaped significantly by the use of pharmacogenomics. Ultimately it will be possible to go not only for an individualized health therapy but also for a predictive/preventive care. Individual genetic differences in

response to specific dietary components or pharmaceuticals have been known for years, but genetic information will be used in future to understand the reasons for individual differences in response to specific nutrients and dietary patterns, or to pharmaceuticals. In the US, survey results indicate that nearly half of Americans are ready to use diet-related products tailored to their health needs based upon their genetic make-up. The consumer would be willing to pay up to US\$ 400 for a nutrigenomic test (6). Future generations could be provided with a personal genetic propensity profile for illness and disease soon after birth. A diet could be formulated that includes specific needs, from *'farm to fork'*, in order to prevent or retard disease progression.



PHARMACEUTICALS FROM PLANTS

Since beginnings of civilization, plants or essential ingredients from plants have been used for health reasons, very often combined with religious aspects. Until today, a European best seller is a book from Maria Treben (1907-1991) titled: "*Health through God's Pharmacy*" - "*There is a Plant for Every Illness!*" (7). During the last hundred years, plant-based ingredients have been extracted, purified and finally chemically synthesized in order to improve human health and to save life. Natural products were often the blueprint for the successful chemical synthesis of highly active pharmaceuticals. Aspirin®, for example, is a synthetic version of salicin, from the bark and leaves of willow trees (figure 1).



But now, at the beginning of the Third Millennium, new cutting-edge technologies based on DNA technologies or nanobiotechnology are available for improving human health and pleasure in future.

TRANSFORMATION OF PRODUCTION OF PHARMACEUTICALS

In 2005, 84 biopharmaceuticals were on the market, serving 60 million patients worldwide for a cumulation market value of US\$ 20 billion. At the moment, worldwide 500 biopharmaceuticals are undergoing clinical trials, 378 are in Phase I & II, and 122 in Phase III. Six to seven new large-molecule drugs will reach the market per year in the common years (figure 2) (8). In 2010, nearly 50 percent of all new approved pharmaceuticals will be of biotechnological origin, if regulatory guidelines are clarified. Insulin is a good example of how pharmaceutical production has been transformed. Insulin was first isolated in 1923 by Farbwerke Hoechst AG (now Sanofi-Aventis) from the pancreas of pigs; in 1984, company researchers succeeded in producing insulin from genetically modified *E.coli* bacteria. Today,

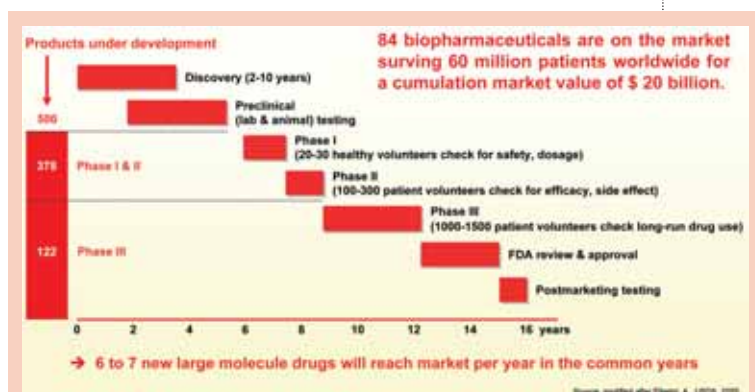


Figure 2. Worldwide 500 biopharmaceuticals in clinical trials, 2005

SemBioSys, Calgary is producing insulin in safflower by plant bio-pharming (9). Insulin is needed by 200 million people (market value more than US\$ 7.2 bln) worldwide. The demand for this life-saving drug is expected to almost quadruple to 14 metric tonnes over the decade. The company announced that by 2015 it will be able to satisfy about a third of the demand from safflower crop grown on 4,000 to 8,000 hectares, if the clinical trials are running well and there is a government-approved product available for sale by 2009. There have also been significant developments in pharmaceutical production in China. Powerful R&D biotechnology clusters have been built up in Shanghai, Hangzhou, Beijing, Guangzhou and Pudong. Pudong, "*The pharmaceutical city of China*", is one great pharmaceutical complex - rather like Frankfurt once was in Germany ("*the apothecary of Europe*"). Pharmaceuticals will be produced here in future for both China and the rest of the world. Biotechnology is one of China's key areas of activity. The research targets are ambitious and rather remarkable. Furthermore, there is another biotechnology-center showing up in Central America. Cuba is concentrating on the biotechnological production of biopharmaceuticals. Up to now, Cuba is offering 38 biopharmaceuticals and nearby 40 new products should be under development.

PLANT-MADE PHARMACEUTICALS (PMPS) / PLANT BIO-PHARMING / PHARMA-FARMING

Pharma-plants are genetically modified plants used for producing pharmaceuticals or industrial substances instead of for food or animal feeding stuffs. The resulting products are known generally as "plant-made pharmaceuticals" (PMPs). PMPs provide several advantages over traditional production of biopharmaca: they can be produced at significantly lower costs and in higher volumes; they avoid risks associated with animal-based products (e.g., mammalian infection); they can be stored by drying rather than expensive and energy intensive refrigeration; and they can be delivered in alternative modes (e.g., oral vaccine rather than by needle) that are often cheaper, safer and more convenient (10).

MolecularFarming.com titles: *Molecular Farming Worldwide "Worth US\$ 100 Billion by 2020"* and invites people to learn about how global health and wellbeing will all be improved by this new type of industry (11). PMPs - protein therapies including antibodies and enzymes - open up promising ways of addressing medical needs. However, there are potential challenges facing the PMP industry - some of them come from the Pharma/BioPharma industry: "*I'm from Texas ... if it ain't broke, don't fix it.*" - Pharma/BioPharma believes fermentation technology is sufficient; "*I'm from Missouri ... show me.*" - Pharma/BioPharma will not believe in PMP technology until a therapeutic protein based on this technology comes to market; "*I'm from BioPharma ... we like bioreactors made of stainless steel or glass-lined vessels in a building, thank you.*" -

Pharma/BioPharma operates within a certain comfort zone. Pharma-farming is not only done with crops, but in bacteria, yeasts, algae, fungi, insects, and animals as well. *International Herald Tribune*, March 27, 2006 published the head line: "*Healthy Bacon, Anyone? Cloned pigs grow to heart-friendly design!*" (12). Cloned pigs that make their own omega-3 fatty acids, potentially leading to bacon and pork chops, those might help your heart. It will however be years before such products make their way to the market, if ever. Bayer AG is committed to the development and production of PMPs. Bayer Innovation GmbH (BIG) which is a wholly owned subsidiary of Bayer AG is convinced that plant biotechnology will become a key driver in the development of healthcare products that

are: specialized, cost effective, and sustainable. In January 2006, BIG acquired the biotech start-up ICON-Genetics and its cutting edge technologies for producing biopharmaceuticals in plants. BIG's product focus is plant-produced proteins for application in areas such as: pharmaceuticals, vaccines, non-pharmaceuticals - industrial enzymes and other proteins (13).

TRANSFORMATION OF CROP PRODUCTION / AGRICULTURAL PRODUCTION

That biotechnology has brought changes to agriculture in a very short time is now obvious. In the last 10 years since their first commercial introduction of transgenic crops, and today, 400 million hectares have been cumulatively grown across 21 countries worldwide. In 2006, over 8.5 million farmers grew GM varieties on 102 million hectares across the world (14). The first generation of genetically modified crops has served the interests of the farm sector, modifying genetic inputs to manage agronomic problems such as weeds and insects. The second generation of GM crops seeks to address the interests of end users, by improving nutritional and quality characteristics of food, feed, fibre and fuel. The third wave aims to "bio-manufacture" pharmaceuticals, vaccines, and industrial compounds in common crops and plants (15).

Within the next 10 years, a computer model of a "virtual plant" that simulates the molecular functioning of a common plant may be used to understand plant physiology and select genetic modifications for establishing favourable traits in a more purposeful way. In North America, over 300 bio-pharming field trials - with a rising tendency - have been performed in corn, soybean, tobacco, rice and other plants. Crops and other plants are producing monoclonal antibodies, vaccines, peptides, hormones, enzymes, growth factors, vitamins and co-factors (16). Until now, no pharmaceutical therapy products (other than laboratory chemicals) obtained from transgenic plants have become commercially available or have found use in medical practice. Apart from laboratory chemicals, no pharmaceutical therapy products obtained from transgenic plants are available at present anywhere in the world. At the moment about ten substances from transgenic plants (corn, tobacco, potatoes) are undergoing clinical trials - commercial cultivation seems very likely in the near future. PMPs via crop biomanufacturing, and especially the production of therapeutic proteins, are attractive because of the potentially large cost savings that could result from using high-yielding and easily cultivated crops. One vital condition will be to prevent contamination of food and feed by PMPs. This means that a failsafe containment and segregation program must be put in place (8). In 2006, the US National Corn Growers Association published: "... there is a long-term opportunity for farmers to grow value-added products from biotechnology and extracted from plants. Pursuit of this new technology platform holds great promise for society. Some biotechnology products require extensive management. Trained and certified growers must have the skills and ability necessary to produce these crops with proper audits. Containment and isolation of PMPs are critical issues that must be resolved in order to protect traditional markets, and realize the promise of this technology" (17). Relevant containment standards for a PMP field release, such as those for maize producing a therapeutic protein, have been established by APHIS (Animal and Plant Health Inspection Service) in the US. To overcome all these problems, some companies in North-America are going for so called "underground crops", modified crops are grown in crop-growth facilities inside former limestone mines several hundred meters below the earth's surface. A controlled-environment production is realized in which all the inputs required for plant growth - light, temperature, carbon dioxide and humidity - are regulated to maximize growth and to produce

PMPs. The underground facilities design incorporates safeguards to prevent any release into the wild of plants genetically modified to produce pharmaceutical agents (18). Last but not least, benefits and risks associated with the production of PMPs must still be communicated to the public early to maximize social acceptance (19).

NANOBIOTECHNOLOGY

A drug is typically a molecule with a particular arrangement of atoms fitting very exactly into a larger arrangement and influencing its function. Drugs are the result of a reductionist approach in biology. Nanotechnology and nanobiotechnology open the way to multicomplex solutions in many areas, including food, health and healing. It is not generally realized that nature has been creating nanostructures for billions of years. Biological systems are an existing proof of molecular nanotechnology. Nanobiotechnology enables mankind on a nanometre scale: to make use of nature's own constructional plans and arrangement principles; to produce biological active therapeutic ingredients; to create bio-compatible and bio-functional materials; to produce bio-sensors and biochemical sensors relevant for e.g., pharmacy, medical technology, food technology, or bio-informatics. A short report titled "Nanotechnology in Agriculture and Food" is given via the European Nanotechnology Gateway in 2006 (20). To date, 180 complete genomes have been published and more than 800 other genome projects are on the way to being identified. The genome and key gene functions of practically all major crop plants and medical plants will have been analyzed in the next five to ten years. A comparative analysis of relevant species on the molecular level will be established. The outcome of all this research will help us to develop new active ingredients for improving nutrition and health.

VISION 2025

For success in improving human health and human life, we need courageous scientists, politically far-sighted decision makers, social transparency and public acceptance. In the end, we need to develop and to implement an ethically integrated management of genes following the vision: 'To understand the dialogue of genes and develop it further - to decipher, marvel at and understand nature's primary language, to add to it with a sense of responsibility and to make use of it in an ethically acceptable way' (21). Finally, from a personal perspective, over the last 25 years working in crop protection and crop production, I found the challenge of contributing to the world's food production extraordinary rewarding. It was and is a pleasure and privilege of working with some of the finest scientists, engineers,



and leaders in the field of safeguarding crop and healthy food production challenged, guided and encouraged by the outlined vision.



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