# Biotechnology – Safety, Health and Environmental Aspects

## Roche Position

In many countries, biotechnology, in particular in conjunction with the use of genetically modified organisms, is a topic that has led to considerable debate. The controversy most frequently centers on "green biotechnology", i.e. the use of biotechnology in the production of food and feed. "Red biotechnology", in contrast, i.e. biotechnological applications in the medical field, including processes enabled by genetically modified organisms, enjoys a more positive image as it has proven indispensable for the production of medicines and vaccines that have brought great progress in the prevention and treatment of medical conditions.

Roche views biotechnology as a technology that opens up opportunities for developing innovative new therapies of high quality for unmet medical needs. Roche is therefore convinced that biotechnology must be further fostered.

Furthermore, biotechnology has the potential to replace certain chemical processes and can make them more ecologically friendly and thus more sustainable. Roche actively explores such opportunities.

At the same time, Roche is fully aware of the risks involved in developing new products and technologies and of the need to be cautious when utilizing them. Roche is therefore carefully monitoring all biotechnological products and processes with regard to both their therapeutic use and their potential impact on workers and the environment. Roche is convinced that this care must be exercised not only in the production and use of innovator/originator products but also for so-called biosimilars or follow-on biologics (www.roche.com/sus_eth_bios.pdf )

The special importance of biotechnological processes in the production of pharmaceuticals can be ascribed to the following three advantages:

- Biotechnological processes are capable of producing molecules so complex that it would be very difficult or even impossible to synthesize them chemically.

- Biotechnological processes allow the synthesis of molecules in a single process step that would require several steps if conventional chemical synthesis were chosen.

- Biotechnological processes can be safer and more ecologically friendly than comparable chemical processes.

The significance of biotechnology in the Roche Group has increased tremendously in recent years. Many of Roche's top selling products are being produced with the help of biotechnology.

Roche clearly states in its Corporate Policy on Safety, Health and Environmental Protection (SHE) that it handles SHE matters with the same sense of responsibility, and just as methodically, as issues of quality, productivity and

cost-efficiency. (http://www.roche.com/sust-se-policy.pdf )

**Safety**

For the commercial production of pharmaceuticals, Roche's biotechnological processes use micro organisms or cell lines exclusively from the lowest possible risk group, which includes only agents that, by definition, "present no or a low individual and community risk". They are not pathogenic to humans and animals and have no adverse environmental impact.

In research and development, and in certain processes used for the commercial manufacture of diagnostic tests, micro organisms may be used that can cause disease. In handling these agents, Roche strictly complies with the appropriate biosafety standards recognized across the world. Genetically modified micro organisms and cells are generally classified in the same risk group as their naturally occurring variants, although they are often dependent on a protected environment and die when released. Roche complies with all pertinent regulations and additionally performs individual risk assessments based on the precautionary principle.

Unlike most classical chemical processes, biotechnological transformation ("upstream") processes take place in an aqueous environment. This eliminates the risk of fire or explosion associated with certain solvents frequently used in chemical syntheses. The use of toxic chemicals in biotechnological process steps is limited, as such chemicals could easily have an adverse effect on the cells involved.

Organic solvents still play a role in some "downstream" biotechnological processes. They are used to extract certain products from the fermentation broth and to purify them.

**Health**

Small amounts of biotechnological products may be taken up by the worker during occupational handling. Enzymes, a typical class of biotechnological products, are potent allergens, and there are numerous reports of work-related allergies, in particular from the food, feed, paper and detergent industries. Concerns about the potential of other biotechnological products used in medical treatment to cause work-related allergies have so far not proven justified. But vigilance is needed and applied.

"Upstream" production processes must be strictly protected from outside contamination. This protection must also be guaranteed "downstream" because many of the biotechnologically manufactured drugs are peptides or proteins, which are typically administered by injection and must therefore be protected during manufacture. Such operational necessities help prevent exposure of workers to these processes and their products.

Health surveillance is important to ensure that no adverse health effects occur in the workers or that they are detected early if they do. Evaluation of these surveillance data has shown that the protective measures taken at the workplace are effective.

One of the most sophisticated groups of commonly used biotechnological medicines are monoclonal antibodies (MAbs). MAbs are very effective drugs, as they are designed and developed to target the diseased organ directly and

exclusively. For this reason, often no effects of the drug are expected in healthy individuals. Side effects in patients are generally mild and predictable. However, there are examples that indicate that serious unexpected effects can occur due to MAb administration. Therefore, Roche handles this class of drugs with all necessary safety measures, as appropriate to any Roche product.

**Environmental Protection**

Where very complex and large molecules must be synthesized, there is often no alternative to biotechnology. These processes are known to consume significant amounts of water and also energy, e.g. for handling the large volumes of water and recovering the solvents used in the "downstream" processes. Efforts are therefore made to reduce energy consumption and water use. Clear targets are set for this purpose. For example, Genentech – a member of the Roche Group – has made a commitment to reduce its water use and $CO_2$ emissions (mainly from energy conversion) per kg of product by 10% between 2004 and 2010. Roche has made similar commitments for the overall Group activities. New biotechnological installations are already 50% more energy-efficient than the older ones.

In several cases, chemical and biotechnological processes have been compared for ecological impact caused by the manufacture of the same product (refer to example attached). In summary, the biotechnological processes performed somewhat better with regard to the consumption of raw materials, water, energy and waste, as well as to other process emissions. The main ecological advantage lay in the nature of the raw materials and the solid waste. Whilst the consumption of raw materials and production of solid waste in the chemical processes is actually lower, the overwhelming majority of the raw materials in the biotechnological process come from renewable sources and most of the waste is biomass that can be composted. The treatment of waste streams is optimised for each process, ensuring state-of-the-art biological safety but at the same time avoiding an overall negative environmental impact due to unnecessary energy consumption.

**Further information sources**

The topic of biotechnology has been addressed a number of times in the annual Roche Group Reports on safety and environmental protection and the following sustainability reports.
http://www.roche.com/corporate_responsibility/principles/reporting_and_indices.htm .

Roche has also published various documents on biotechnology
http://www.roche.com/research_and_development/innovation_and_technologies/biotechnology.htm .

**Contacts**

Peter Schnurrenberger, Corporate Safety, Health and Environmental Protection (CSE),
peter.schnurrenberger@roche.com, +41 61 68 85213, Basel

Andreas Flückiger, Corporate Health Protection (CSEH),
andreas.flueckiger@roche.com, +41 61 68 83738, Basel

**Comparison of a typical chemical synthesis of a small molecule with a biotechnological process to manufacture the same substance (bacterial production system, both upstream and downstream processes included)**

| | Chemical process | Biotechnological process |
|---|---|---|
| Number of process steps | 4 | 1 |
| Raw materials (kg per kg of product) | 6.980 | 10.340 |
| Renewable | 1.100 | 9.230 |
| Non-renewable | 5.880 | 1.110 |
| Water ($m^3$ per kg of product) | 3.035 | 6.817 |
| Cooling water (no treatment) | 2.910 | 6.800 |
| Process water (treated) | 0.125 | 0.017 |
| Energy (GJ per kg of product) | 0.207 | 0.202 |
| Electricity (kWh per kg of product) | 7.428 | 15.224 |
| Steam (t per kg of product) | 0.056 | 0.041 |
| Gas ($m^3$ per kg of product) | 0 | 0.444 |
| Solid waste (kg per kg of product) | 1.110 | 2.300 |
| Chemical waste | 0.330 | 0 |
| Biomass (composted) | 0.780 | 2.300 |
| Emissions to wastewater (kg per kg of product) | 3.700 | 1.290 |
| Emissions to air (kg per kg of product) | 0.865 | 11.507 |
| $CO_2$ | 0.850 | 11.500 |
| VOC and organic dust | 0.015 | 0.007 |

In conclusion, energy consumption is virtually identical with both processes. The fermentation process leads to no

VOC emissions. The fermentation wastewater contains only inorganic salts and readily degradable biomass residues. Water usage in the fermentation process is twice as high as in the chemical process, but over 99.75% of this water is cooling water that remains uncontaminated (96% in the chemical process).

The main ecological advantage of the biotechnological process is the fact that a much larger portion of the raw materials comes from renewable sources, and the $CO_2$ and biomass generated are returned to the natural processes that produce glucose from $CO_2$ and utilize the biomass as a nutrient source in the soil.

This Position Paper was approved by the Corporate Sustainability Committee on April 29, 2009 and entered into force the same day.