USE OF CELL BIOTECHNOLOGIES FOR INDUSTRIAL PRODUCTION OF PLANT RAW MATERIAL FOR PHARMACEUTICAL APPLICATIONS

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Biopharmaceutical manufacturing, because of its complex nonlinear nature, is fraught with a myriad of process variations that can impact safety and efficacy of the drug. Since the introduction of concepts such as process characterization and design of experiments (DoE) over two decades ago, the biopharmaceutical industry has created and demonstrated considerable expertise in unravelling how the process affects the product. However, the role of raw materials (RM) has been somewhat overlooked and as a result has become the primary source of variability in process performance and product quality. The growing significance of the role of raw materials in the process control strategy is evident from the ICH Q8 guideline, which suggests that in the Quality by Design (QbD) framework the manufacturer must understand all sources of variability including the raw materials.

More than half of all medicines contain plant-based substances. 80 - 90% of the world market for plant raw materials is provided through the picking up of wild plants, many of which are rare and endangered species. Plant cell culture can serve as a source of renewable high-quality raw materials; however, the biomass of cell cultures is not an analogue of a traditional plant raw materials. Plant cell culture is a unique, experimentally created biological system: it is a population of proliferating dedifferentiated plant cells. But upon creation of a good producer strain and optimal technology for its cultivation, it can surpass traditional raw materials.

We approaches have been developed for the efficient creation of producer strains, and some of these has been obtained - in particular, strains of various species of *Ginseng, Dioscorea, Ajuga, Poliscias, Tribulus, Taxus,* and investigated their main growth and biosynthetic properties.

Using LC-ESI-Q-TOF-MS (liquid chromatography electrospray ionization quadrupole time-off light mass spectrometry) it was found that all investigated plant cell cultures formed biologically active secondary metabolites; however, their composition and quantitative content were different from those of intact plants.

Plant cell culture of *Panax japonicas* has a high content of ginsenosides (3 – 5% on dry biomass), with unique composition. “Acidic” ginsenosides appear (malonyl derivatives of ginsenosides of the Rb group), as well as a number of “minor” glycosides such as the Gypenoside XVII. Plant cell cultures of *Dioscorea deltoidea* (more then 10 lines) contain high

level (6 - 10% on dry biomass) only furostanol but no spirostanol glycosides. Furostanol glycosides has many useful properties - antioxidant, sex-stimulating, adaptogenic, etc. - important for pharmaceutical use.

Plant cell cultures of *Ajuga reptans* and *Ajuga turkestanica* contained only very small amounts of ecdysteroids, but significant amounts of phenylethanoid glycosides were found in them. Curiously, a similar situation was shown for cell cultures of different species of *Digitalis*. No cardenolides were found in these cultures either, but phenylethanoids were present.

Thus, plant cell cultures can be promising sources of different biologically active substances of plant origin, and in the case of using an effective producer strain, can be high-quality plant raw materials for pharmaceutical use.

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