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Development and Design of Upstream Processes for the Manufacturing of biogene Therapeutica and Vaccines based on Molecular Farming

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1 GENERAL INTRODUCTION

Future challenges for the pharmaceutical industry

Global competition, trends in medicine and technical innovations require significant changes in the development and manufacturing of pharmaceutical products. Smaller batch volumes, a more sophisticated range of products and efficient, flexible processes need to be implemented in order to meet the future demands.

The potential of „Molecular Farming“

The term „Molecular Farming“ describes the heterologous expression of pharmaceutical proteins in plants. This technology has emerged as viable alternative to the conventional expression systems used, like bacteria or mammalian cells, through various optimizations and innovations regarding the capability and yield of synthesis in the last two decades. Several experiments, current industrial projects and commercial products have shown the general suitability of plants as efficient production systems for the pharmaceutical industry, which seem to fit the requirements set above really well.

2 OVERALL OBJECTIVE AND PURPOSE

With regard to the potential of Molecular Farming, a plant based, flexible, multi-purpose manufacturing process for the production of therapeutics and vaccines is developed and designed.

The general purpose of this work is:

i) The Identification of potential products and processes of the mentioned technology

ii) The development respectively adaption of specific unit operations and subsequently analysation following the Six Sigma methodologies

iii) The design and development of basic process flow diagrams and specification of measures to realize potential chances or reduce immanent risks

3 SCIENTIFIC PRINCIPLES AND METHODS

The following scientific principles and methods are applied:

- Plant expression technology, systems and potential products;
- Process development and process design methods;
- Processes, methods, and tools of Total Quality Management as integral part of Quality-by-Design (QbD), Lean Management / Six Sigma in particular core process define, measure and analyze;
- Factor and criteria design as well as investigation, definition, measuring, and analyzation of process and unit operations.

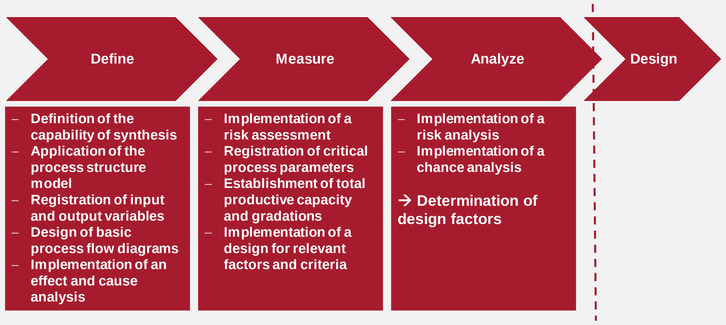

Fig. 1: Characteristic phases of the applied DMADV process and corresponding methods used to develope and design a process for the manufacturing of biogene active pharmaceutical ingredients

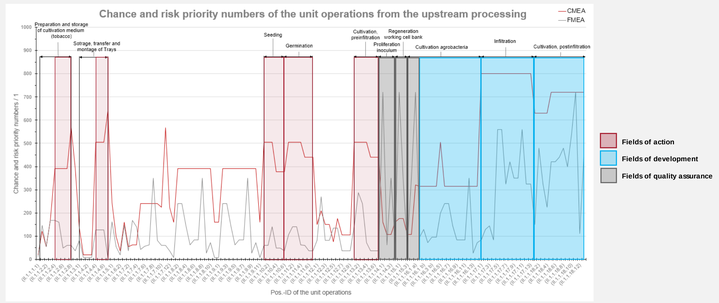

Fig. 2: Exemplary plot of the chance and risk priority numbers against the corresponding unit operations of the upstream process, including coloured highlighting of the specific categories identified by relational considerations of both priority numbers

	Potential design aspects					
Field of development	**Process**	**Apparatus technology**	**Facility layouts**	**Building technology**	**Automation / monitoring**	**Inbound / outbound logistics**
Dilution of the bacterial suspension	No further actions	i) Distribution station ii) Recipe control iii) In-line-dilution (if necessary static mixer) iv) Capability for CIP / SIP / DIP	Arrangement planning including storage tanks if necessary, alternative solution is the direct connection of the distribution station with the infiltation chambers	No further actions	SCADA incl. Management of recept controls for preparation, dilution and infiltration	No further actions

Fig. 3: Specific design aspects of an exemplary field of development divided in six different categories

4 APPROACH

Results

Based on the scheme of the DMADV process according to the approach Design for Six Sigma, critical requirements for the process were formulated and appropriate methods were identified (see figure 1).

Magnifection, a technology for the transient, heterologous protein expression mainly in tobacco plants, is particularly suitable for the strived product spectrum, productivity and general application. Based on this method, an upstream process, including selected sections of the bioseparation, was developed by the use of a process structure model and divided into modular sections with corresponding elements like process steps and unit operations (see figure 4).

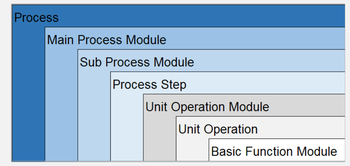

Fig. 4: Structure of the process model used to develope the pharmaceutical manufacturing process

After the identification of relevant input respectively output variables and critical process parameters the corresponding unit operations and material flows were visualized in the form of a basic process flow diagram. Subsequently, the productive total capacity of the process was established, a concept for the simultaneous, capacitively flexible production of different active pharmaceutical substances developed and the process correspondingly balanced.

Critical requirements for manufacturing processes in the pharmaceutical industry have been identified by a cause and effect analysis. Consideration was given to developments such as the design of multi-product plants based on the concept of adaptability and regulatory requirements, which then were registered in the form of criteria catalogs. These formed the basis for the subsequent risk and chance analyzes of the unit operations of the developed process.

In this way the critical points of the process were recognized and specific design and risk measures could be defined. By relational considerations of corresponding chances and risks relevant process sections could furthermore be assigned to specific categories, that were divided into fields of action, development and quality assurance (see figure 2). Based on these categories, specific recommendations for the future implementation of previously mentioned measures could be formulated (see figure 3).

Conclusion

The scientifically elaborated process structures, their balancing and the measures discussed in the course of the consideration of risks and chances are intended as a basis for the establishment and realization of a flexible manufacturing process based on the heterologous expression in plants. This includes the future design of process flow diagrams, corresponding apparative design and layout planning.

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