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havior the process change has to be considered major. This may result in a PLA amendment, if in a limited clinical study the therapeutic dosage can be adjusted, or if not, in a new PLA with new clinical studies.

Influenced by these regulatory requirements, decisions for process changes are dominated by the concern for whether the process change might influence product identity or quality and by the economic value achieved by the process change. Economic value in turn is determined by the expenditure for process development on the one hand and the economic and/or quality improvement in comparison to the market potential of the biopharmaceutical on the other.

In conclusion, potent protein analytical methods are available and will be further improved for the detection of changes in product quality initiated by process changes. These analytical tools are suitable for guiding process development.

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Requirements and Validation of a Biotech Multipurpose Plant

Hermann Allgaier*

As biotechnical derived products become more and more available through the pipeline of the biopharmaceutical industry the need for biotechnical manufacturing plants in which more than one product could be handled is of utmost importance with regard to flexibility and process economics. However, to deal with living organisms and associated impurities thereof requires special attention concerning the prevention of potential crosscontamination in all involved areas such as inoculum, fermentation, harvest, downstream processing, formulation and aseptic filling/lyophilization. The requirements of a mammalian cell culture facility operating in a multipurpose mode with special emphasis to the validation strategy guided by the new FDA form 3210, Application for Establishment License for Manufacture of Biological Products, is given.

General Situation and Regulatory Requirements

The increasing number of Investigational New Drug Applications (IND's), Product License and Establishment License Applications (PLA's/ELA's) and finally the increasing number of approved biologics has put pressure both on the regulatory bodies and the biopharmaceutical industry to define the requirements for a biopharmaceutical plant operating in a multipurpose mode. What does make biotech manufacturing so unique if compared with other branches like the bulk pharmaceutical chemical manufacturing and the finished dosage form manufacturing where multiuse manufacturing is a given for decades? The fear from the selfreplicating mechanism of living organisms is the main reason for doubting that cell lines could be handled simultaneously in a manufacturing facility. In addition, host cell line derived impurities like mycoplasma and exogeneous and endogeneous viruses must be considered thoroughly. It is both the possibility of a biochemical crosscontamination and the possibility of a biological crosscontamination which requires special attention with regard to the cultivation of more than one cell line in an existing facility.

According to 21 CFR 600.11 spore bearing organisms must be handled in a separate facility [1]. This is also true for the fermentation of penicilline which is regulated in the 'Guide to Inspection of Bulk Pharmaceutical Chemicals' [2] and the Code of Federal Regulations 21 CFR 211.42 [3]. In contrast, the European 'Supplementary Guidelines for the Manufacture of Biological Medicinal Products' [4] state that 'parallel production using closed systems of biofermentors may be acceptable for production such as monoclonal antibodies and products prepared by rDNA techniques'. In the United States, a 'White Paper' named 'Multi-Use Manufacturing Facilities for Biologicals' [5] issued by the Pharmaceutical Manufacturer's Association (PMA) and the subsequent discussions led to the acceptance of biological multiuse manufacturing facilities indicated by the form 3210 issued by the FDA 'Application for Establishment License for Manufacture of Biological Products' in which a statement must be made 'whether this is a multiproduct facility' [6]. An accompanying document named 'Points to Consider on the Use of the revised ELA Format' will be issued soon and defines the requirements in detail [7].

Very often, the approach of 'campaign manufacturing' *vs.* 'concurrent manufacturing' is discussed as the two main manufacturing strategies in biotech multiuse facilities. However, in a given facility consisting of the four main areas inoculum, fermentation and harvest, purification and final formulation the strict requirement of campain manufacturing as being defined as 'Processing of more than one product in the same facility and/or equipment in a sequential manner. Only one product is present in the facility at a time' is of less importance because product changeover times between 40 and 70 days depending on the manufacturing scale and the used mammalian cell line are not economically feasable. Therefore, provisions must be taken into account allowing either the parallel cultivation and purification by the use of closed systems in common areas or by means of spatial separation in case of working with open systems. The layout of the manufacturing facility is, therefore, of utmost importance for the concurrent manufacturing of more than one product.

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Specific Requirements for Biotechnical Operations

In the inoculum area, where handling of cell lines takes place in open systems under laminar air flow units the cultivation of more than one cell line can be achieved by the installation of several inoculation suites. By this, all required operations such as inoculation, cultivation, transfer and sampling could be done independently by the spatial separation of the different inoculation suites. The fermentation of mammalian cell cultures can be conducted simultaneously due to the use of closed systems. However, special attention has to be drawn to inoculation, sampling and transfer procedures. The purification and formulation of proteins should be carried out subsequently with only one product at a given time point in the downstream areas. The personnel and material flow in the manufacturing facility should be optimized, so that the interaction between 'clean' and 'dirty' is minimized. The use of different autoclaves for inactivation and sterilization purposes with double doors enables a proper material flow in cleaning areas.

All manufacturing equipment in the facility should be characterized as disposable, dedicated and non-dedicated. An intensive status labelling, colour codes for different products and logbooks for major equipment are general GMP-requirements which are of major importance in a multiproduct facility. Dedicated and non-dedicated production equipment must be stored in general storage areas under controlled conditions, so that floors and hallways could be left empty. Even though this seams to be obvious, existing monopurpose plants which are used later on for the manufacture of more than are product often lack spacious general storage areas.

Systems for the generation, storage and distribution of Purified Water and Water for Injection as well as Clean Steam and Compressed Air generation and distribution are important utilities from the general GMP point of view. Critical utilities in multipurpose manufacturing plants are the Heating, Ventilation and Air-Conditioning (HVAC) systems, the Cleaning-In-Place (CIP)-units, the Steaming-In-Place (SIP) systems and the sewer and inactivation systems. One important feature of the HVAC-system should be the capability of running specific areas like the inoculum area in a non-recirculating once-through mode due to the potential distribution of aerosols all over the manufacturing plant. Other areas like the formulation area could be run in a recirculating mode. To gain flexibility it could be advisable to install more than one HVAC-unit for the manufacturing plant. The separation of the fermentation and initial purification area from other parts of the facility by the installation of airlocks could further reduce the potential for crosscontamination. Air pressure differentials directed in general from clean areas to less clean areas further contribute to a controlled environment within the facility. The room classification strategy should take into account a risk analyses with regard to the work carried out under open or closed conditions. Therefore, under normal circumstances the highest room classification should be applied for the inoculum and form formulation areas whereas the fermentation area could be run under less strict, but still defined conditions [8][9].

A validated Cleaning-In-Place system in combination with properly selected cleaning agents and analytical assays for the determination of cleaning agent residuals, product related and product derived impurities is a key element to run a multiproduct facility under control. The recycling of cleaning solutions could be questionable if only one CIP unit exists for the different manufacturing areas. The dedication of CIP units to distinct areas such as fermentation, initial purification and final formulation is advantageous if capacity requirements allow such a separation. In these cases, the final rinse water (WFI) from the previous cleaning step could be used for the pre-rinse cycle of the next cleaning step. The sampling for the cleaning validation study must consider both final rinse samples as well as surface analyses including a proper correlation between the results of the two sampling methods. Residue specific methods could be directed against the product and the cleaning agent whereas nonspecific methods like the determination of the USP water quality and the determination of the Non-Purgeable Total Organic Carbon (NPOC) can give an overall assessment of the cleanliness status of dedicated and non-dedicated equipment. Final rinse investigations are suitable for changeover measurements whereas swab samples normally are taken during the validation phase. Specifications must be scientifically sound and could be determined only on an individual case by case decision. However, the recently published Guide to Inspections of Validation of Cleaning Processes states that, 'some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 ppm, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue' [10].

Areas where growth, preparation, and storage of the Master Cell Banks and Manufacturer's Working Cell Banks take place attract more and more the attention of the regulatory authorities. One important decision which must be made during the early phase of a project is the decision when a cell line switches from the experimental status to a full GMP cell bank status. Therefore, the new form 3210 requires the 'indication where the growth, preparation and storage of the Master Cell Bank or Seed and Manufacturer's Working Cell Bank or Seed take place, including areas where validation was performed on the host systems' [6].

The generation of fermentor inoculums is susceptible to contamination since it often requires open transfers. Therefore, the already described work in different suites under environmentally controlled conditions is highly recommended. In addition, a well thought-out categorization and strategy for the storage of the different cell banks is suitable to minimize the potential for operator errors and derived mix-ups. Thorough changeover procedures in between cell lines cultivated subsequently in an inoculation suite must be followed and include cleaning and disinfection measurements, replace of product or cell line dedicated equipment and documentation, equipment tagging and operator instructions. The required validation of transfer procedures could be achieved by media runs following the general thoughts of the 'Aseptic Filling Guideline' [11].

In the fermentation area the cultivation of more than one cell line at a given time point must be preceded by the validation of the integrity of the closed systems. The mere claim of sterility is not sufficient to proof closed systems integrity. A risk analysis considering all entries and exits of the fermentation vessels could be very helpfull for the design of the validation protocol. The media runs should mimic as much as possible the routine fermentations including addition of additives and transfer procedures. Changeover-procedures include final rinse sampling and testing under equipment quarantine, exchange of product dedicated equipment like air filters, change of equipment tagging and operator instructions for the fermentation of the new cell line.

It is noteworthy that the new form 3210 issued by the FDA does not mention the term closed systems with regard to isolation, purification and final formulation in downstream processing operations

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[6]. The PMA White Paper proposed that 'initial purification operations using closed vessels and hard-piping may permit simultaneous processing of more than one product in a suite' [5]. This proposal was discussed several times between the agency and the industry and obviously, the White Paper proposal was not successfull. Therefore, the purification or formulation of not more than one product at a given time point in a purification suite is advised. Special attention should be drawn to the addition of additives to process solutions which must be done under proper environmental conditions. The product changeover program in the purification areas is comparable to the one described in the fermentation area and must follow documented and validated procedures.

Support areas such as media and buffer preparation areas are of less importance with regard to 'biological' crosscontamination. However, they must follow all general GMP requirements to prevent any possibility for errors and mix-ups.

In summary, the requirements for multiproduct manufacturing have been defined and multiproduct manufacturing can and is being done now. Early market entries for new biopharmaceuticals can be achieved and the basis for flexible and economic manufacturing of biopharmaceuticals is given.

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Modelling and Process Control – a Tool for Quality Control and Validation?

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Good Manufacturing Practice (GMP) means having the quality level customers are expecting built into a product. Each step in a manufacturing process must be regulated to ensure that the final product meets the quality and design specifications with respect to identity, purity, and efficacy.

A (biotechnological) production process consists of many steps. Upstream processing, the transformation process itself, and purification steps. The final product quality is dependent on the whole production chain, including storage and shipping. The upstream processing, fermentation and downstream processing interact at numerous points with respect to final product quality.

A transformation process is in principle the stepwise handling of information, basically done by man and machinery. The process control tools maintain and manage the information. On-line measurement allows fast access to process-relevant physical, chemical, or biological parameters. Modern process control keeps the process parameters within the defined range. A stirred fermenter is a closed system in which physical and chemical parameters can be kept constant. Bacteria and enzymes (immobilized or not) are only able to work reproducibly if their parameters for growing or producing are kept constant. Process control enables fermentations (or biotransformations) to be carried out under reproducible production conditions [1]. The resulting biocatalyst is homogenous with respect to reaction behaviour. Consequently, the resulting process time also turns out to be reproducible. This is shown by one example in the *Figure*, from our well-controlled L-carnitine fed-batch biotransformation process. Thus process control contributes to a better defined process. This makes the validation of a process, and, therefore, the establishment of GMP, much easier.

Furthermore, early recognition of deviations in the fermentation can be detected. Process deviations, *e.g.* a phage attack or medium faults can be recognized early. Based on the on-line analysis, process models allow access to non-measurable variables. New instruments are currently being developed to get an insight into a process in order to detect deviations earlier or even to predict deviations. The process information is upgraded enabling counter measures to be taken in time to minimize loss of batches. However, the process control software will have to be validated too!

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