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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?

Markus Rohner*, **Frans W.J.M.M. Hoeks**, **Elisabeth Böhlen**, and **Hans-Peter Meyer**

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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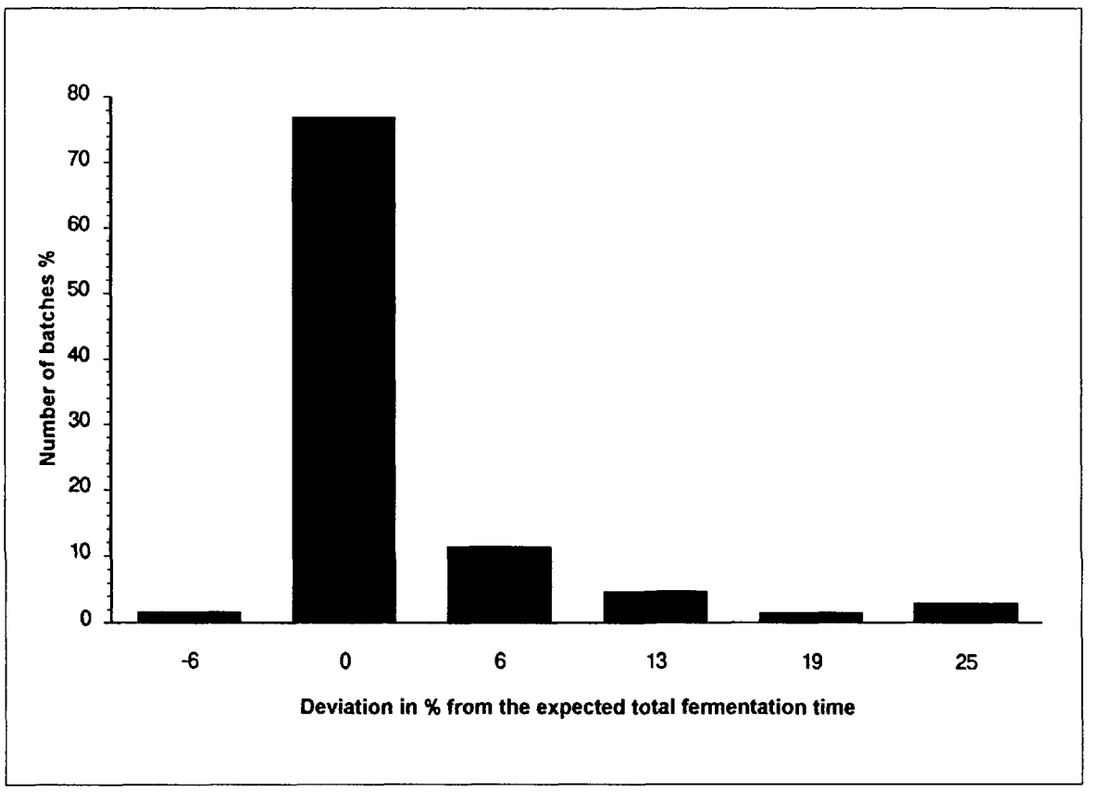

Figure. *Percentage of* L-*carnitine batches* vs. *the deviation from the expected total fermentation time.* 77% of the batches had a relative deviation of less than 3% of a total production time of several days.

In biotechnological manufacturing, sterilisation is a key unit-operation for a GMP bioprocess. However, aseptic monitoring is very time-consuming and depends on tedious off-line analyses. In addition, reasons for contamination are very difficult to locate and identify. The GMP rules must, therefore, be implemented at every level. Extensive experience has been collected over many years of sterile, reliable and safe production in biotechnology. Making use of this extensive experience should turn non-sterility into a minor problem. Thus, obtaining GMP standards concerning sterility of a bioplant is nowadays routine.

If the fermentation broth to be worked up is produced under well-controlled conditions, the downstream processing will be reproducible. Fluctuations in the quality of the transformation process in the fermentation step lead to possible fluctuations in the final product and increase workup costs.

Very often, less process information about the downstream processing is available, since it is considered to be less important. But in almost all fermentations, the downstream processing is the step where the added value of fermentation products is realized. More information about the downstream processing can facilitate the validation. Deviations can be extremely difficult to relate to causes [2]. However, specifications for each step are set to maintain the final product quality and actions are fixed if these specifications are not met. If the causes are not known, counter measures for non-specifications are hard to define and to justify within the GMP framework. Rejection of products can be the result.

For (bio)process development, modelling is very useful for process design purposes [1]. In addition, it is also a tool in order to detect any impact from changed process conditions (medium, water quality and others). It is a future oriented technology with great potential for different applications. Modelling can help validation in order to facilitate process evaluation, *e.g.* minimization of by-product formation.

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