

# Process life cycle in custom manufacturing

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The trend to custom manufacturing in the life science (LS) industry is still ongoing with a growth rate of around 9% per annum, however, the whole business environment has changed quite drastically during the last couple of years. To speed up the new product creation cycle, development time of a new drug (NCE) is reduced from around 120 months to 70-80 months. Most of the pharma companies have initiated special 'faster time to market' programmes. This has reduced the time for process development considerably. The task to adapt and transfer a new process into an existing plant is therefore also a key element of the cross-functional process development team.

Additional time pressure is put on process development and industrial manufacturing by the increased complexity of the new chemical entities (eg multiple stereogenic centres) and a more stringent regulatory environment. Parallel process development activities and close collaboration between development and manufacturing experts has to be adapted in order to achieve the targeted product launch, since process development is now often the bottleneck in the whole LS-product creation cycle.

Lonza Group has taken proactive action in three main areas in order to meet customer requirements. The whole R&D and production organisation was re-engineered three years ago to support the changing business process the best possible way since cross-functional project management is the key success factor. In a second area, reaction engineering tools (like automated lab reactors and chemometric methods) are used for efficient process development and process evaluation. The objective "manufacturing process development" is underlined by job rotations of research chemists in development, process optimisation and manufacturing areas. As a third action, process management software was chosen to support the process life cycle. The software is used for early production site selection, productivity analysis and as a know how transfer tool between different functional departments and production sites.

## Process development technology

Advanced tools are a key to efficient process development. Lonza has identified the following main tools in order to gain more information out of limited lab development time and limited resources:

- Process simulation
- Chemometrics
- Reaction technology
- Chem. screening
- Physical properties.

Computer controlled lab reactors are the main tools for applied reaction technology. The one chosen by Lonza shifted from a pure safety tool to an integrated development tool. Safety data are measured at the same time as mixing, heat transfer or batch/semi-batch studies are performed. Additional on-line sensors like IR, turbidity, pH or off-gas analysis are delivering valuable additional information. Lets point out, that all this information reflects the whole reaction path in respect to time and actions taken throughout the run. This is in contrast to traditional methods, where "a one day run" is judged based on the chemical yield achieved. This is even more helpful, if toxic or irritant compounds like phosgene or others are used as reagents.

Process adaptations have to be carried out in order to utilise existing equipment and reduce investment costs. Such changes have to be validated in detail to ensure specification conform products.

## Knowledge management & communication

The sequential business process (sequence & route selection followed by scale up, trial production, tech transfer and full scale manufactur-

ing) has changed quite dramatically during recent years. The sequential approach had the advantage, that much more information was available at the beginning of the next development stage, but the required time-line was 40-45 months longer than in the parallel development approach.

Due to the compression of the product creation cycle, a much more complex approach was developed out of the sequential process during the last couple of years. Figure 1 shows some possible pathways for process development in the custom manufacturing environment.

The parallel work flow leads to a lot of reiteration of similar tasks like productivity assessments or mass balances after changes in assumptions or newly available knowledge. Since the customer expects a competitive offering at an early stage, siting decisions and investment costs are taken into account much earlier than in the previous, sequential business cycle. Imperative evaluations of synthesis alternatives are taking up more R&D-time, since cost of goods will determine at the end the volume split between different suppliers.

The continuous iteration of similar tasks (e.g. productivity assessment) in cross-functional teams involving engineering, R&D and production planning/site evaluation needs a supporting tool, which transfers data easily within the team and enables improved communication of process changes.

Initial tests were successful in several departments. Data during project evaluation are entered into the system only once. Projects are afterwards simply transferred within the cross-functional team. The software was successfully qualified by several organisational units and implemented for routine operation.

## Outlook

Lonza Group has initiated and implemented successfully several changes to support the new parallel development process together with the application of new, efficient development tools. Even though key areas like "early design to manufacturing", optimal utilisation of existing assets or process robustness are still improvable, the scientific mind-sets of the co-workers adapts now well to the parallel approach, even if all education and training was carried out in a sequential fashion.

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Figure 1. Parallel product creation LS process

