Answering Pharma's Need for Outsourcing – Process 'Intensification' Technology for the Future of Biopharmaceutical Production

PEER REVIEWED

The chemical and pharmaceutical industry will face challenges in the future related to manufacturing costs and lowering environmental impact. Chemical and biopharmaceutical manufacturing need to be modernised, with lower raw material usage, higher yields with fewer resources, more focused manufacturing processes, and reduced manufacturing cost as final results. DSM Pharmaceutical Products, the outsourcing manufacturing partner within Royal DSM N.V. (#1 on the Dow Jones Sustainability Index 2011), a global science-based company active in health, nutrition and materials, is a custom manufacturing organisation offering proprietary (bio)manufacturing technologies, innovations in sustainability, and green chemistry, in R&D and commercial manufacturing services. Application of technologies brings down its manufacturing costs through process *intensification* to offer shorter and more efficient scale-up of (bio)pharmaceuticals, speeding up development, better managing manufacturing volumes and driving down total costs.

In this context DSM challenges conventional process technologies with innovations in process intensification for next generation manufacturing solutions. These innovations range from boosting cell culture titers and utilising alternative starting materials in synthesis routes to increase drug substance yields and continuous flow API production. Biotechnology and (bio)chemistry are applied when working with micro-organisms, enzymes, mammalian cells and organic starting materials to produce novel ingredients and to improve existing ingredients, (bio) pharmaceuticals, and chemicals. With the market facing downsizing in production volumes of certain APIs, smaller batches of high-powered speciality drugs and a need to reduce costs and environmental impact, DSM has invested in multiple synthesis, scale-up and production technologies continuously over time.

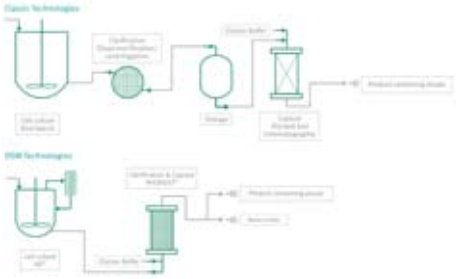
Especially in the pharma outsourcing market a global portfolio of resources is needed to continuously serve changing customer needs and bring real value as the pharma industry shifts business models. In today's market where manufacturing efficiency has become a strategic driver for pharmaceutical companies, contract manufacturing organisations like DSM are responding to provide sustainable solutions with their manufacturing expertise, advanced technologies and regulatory support.

Biomanufacturing (Mammalian and Micro-organism-based)

The three major economic drivers for the development of protein therapeutics manufactured using mammalian cell culture are the cost of goods, time to market approval, and reduction of financial risks associated with capital investments for dedicated production facilities. In mammalian manufacturing, the trend for process intensification has been developing for many years. The productivity of cell lines has been improved by using better production vectors, targeted integration into the hot spots and better use of cell metabolism.

In addition, modern media supports higher cell densities in standard fed-batches, increasing yield output. One way to address these drivers is to improve the efficiency and productivity of the manufacturing processes. This is relevant for new biological entities but even more relevant for biosimilars and biobetters manufacturing. DSM has developed a strong technology portfolio (Figure 1) that enables shorter processing times and a lower cost of goods to achieve this goal. In addition, the manufacturing facility footprint is significantly reduced with the use of these technologies, thereby reducing capital investment and enabling easier investment decision-making.

Figure 1. Flow chart: reduced number of unit operations, intensified processing, and increased output from decreased footprint are all advantages of DSM's XD® and RHOBUST® technologies.



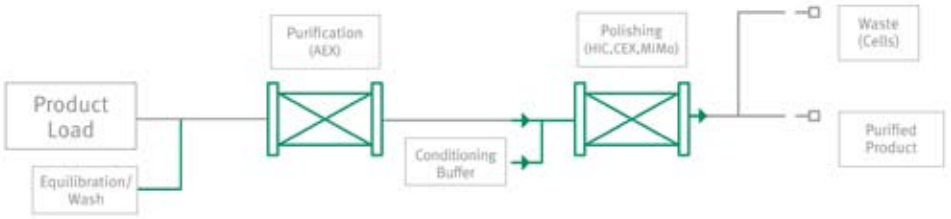
Today 5g/l for antibody production is standard. However, DSM has taken yields to higher levels with a manufacturing process to achieve 5- to 15-fold increases. For example, XD® Technology leads to very high cell densities in a bioreactor, giving significant titer improvement compared to standard fed-batch processes. The XD® process technology combines the benefits of fed-batch and perfusion processes. This technology works in a continuous media feeding mode, with a filtration unit to retain both the cells and the recombinant protein in the bioreactor, while metabolic by-products are continuously washed out. It is demonstrated to be virtually cell line and product independent, as it has been successfully applied to multiple cell lines (CHO, hybridoma, myeloma, PER.C6® cell line) and to multiple product types (monoclonal antibodies, Fc-fusion proteins, recombinant proteins). The XD® process is robust and scalable, while still maintaining consistent product quality. The scale-up of XD® cell culture is possible after minimal process development, which significantly reduces the timelines and costs of the development.

RHOBUST® is a direct protein capture downstream technology which combines clarification and product capture into one single step. Centrifugation, depth-filtration and packed bed chromatography can be replaced by one unit operation, resulting in less preparation and process time. RHOBUST® uses cross-linked agarose beads with tungsten carbide to increase the particle density. Cell removal through centrifugation and/or filtration is made obsolete due to the fact that the crude harvest can be loaded directly onto the RHOBUST® column. Cells flow

through the column, while the product is being captured on the beads.

As an additional effort to achieve further streamlined purification and polishing of proteins as a single unit operation, DSM has developed the Kremer Method™. The Kremer MethodTM is an inline flow-through protein polishing step. This serially-linked flow-through purification for IgG combines 2 chromatography steps in one unit operation (see Figure 2).

Figure 2. Kremer Method™ - Serially-linked flow-through purification for IgGs after product capture.



For example good removal of HCPs (12,000 ng/mg to less than 31 ng/mg using a Mustang Q membrane absorber) and aggregates (3.6% to 0% using Poros HS CEX column) were observed using a ProteinA purified IgG from mammalian source as start material.

Advanced technologies in microbial fermentation-based processes are continuously developed and improved for in-house production processes at DSM. Innovations range from production strain construction and improvement, to fermentation process concepts, and product isolation technologies. These innovations fit classical fermentation products as well as modern biotechnology-based products such as recombinant proteins, advanced scale compatible expression platforms for protein production, various modes of fermentation process execution, and select high-performance product isolation and purification operations.

Synthesis Optimisation and Micro-reactors

Adopting a micro-reactor production platform requires that an outsource partner can demonstrate the knowledge and skill in such manufacturing to take the process from the small scale to the scale required when a customer's product is on the market. Using large vessels to produce pharmaceuticals has a number of disadvantages. Most importantly, large-scale chemical reactions in these large vessels deliver large quantities of unwanted – sometimes dangerous – by-products. These by-products have to be disposed of, resulting in a negative environmental impact. The traditional production method – which also requires heavy use of energy resources and can generate a lot of heat that needs to be cooled – is not very efficient; more solvents, catalysts and other starting materials are needed than is desirable.

A micro-reactor is a continuous tube reactor with a small channel diameter. To reach the desired throughput of such a reactor, it contains thousands of small channels in parallel, each of them surrounded by coolant. In this way, the average micro-reactor can be as small as a small cupboard and can handle 1000-2000 kilograms of product per hour, with yields more than 20% higher than in the traditional large vessels, with a much lower CO_2 footprint and at lower costs. Measured per cubic meter (kg/m^3h) the productivity increases by a factor of 10^3-10^4.

DSM has been working with micro-reactors for more than a decade, and in early 2009 completed full-scale commercial production of an active pharmaceutical ingredient.

We practice 98% of prevailing chemistries and create many active ingredients and intermediates. In our unique convergence of biocatalysis and chemocatalysis, or "innovative synthesis", we are finding faster routes to new drug compounds with more renewable starter materials. DSM route scouting services meet outsource needs for the development of robust low-cost manufacturing routes. Route scouting capabilities have proven to lead to significant cost savings and a better environmental footprint by the reduction of synthesis steps or redesign of synthesis routes, where true innovation is achieved by integration of different cutting-edge technologies developed by DSM and partners.

DSM Pharmaceutical Products business group serves the global pharmaceutical and biopharmaceutical markets, offering manufacturing services, R&D/formulation and technologies for biologics, both cell culture-based and microbial; active pharmaceutical ingredients and intermediates; as well as finished dosage manufacturing. The business group works closely with all DSM pharma interests including DSM Sinochem Pharmaceuticals, Biomedical, and Nutritional Products.

Dr. Fritjof Linz
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Dr Linz started his business career in the downstream processing industry holding different roles in sales, product management and development at Sartorius. Thereafter, he became Head of Marketing & Sales for a microbial scale-up CMO – Devoferm which is a member of the Aventis Research & Development group. From here, Dr Linz moved to a facility & site management organization called InfraServ, which serves the Pharma & Biotech industry. Dr Linz joined DSM eight years ago having responsibilities for large Pharma companies' chemical and microbial CMO business, serving countries like Germany, Japan and others. For the last four years he has been a member of the DSM Biologics sales team with responsibilities for custom manufacturing and technology licensing around the world – mainly Europe. In addition he is the Head of Marketing for DSM Biologics.

Dr Linz has a PhD. in Chemistry at the University in Hannover with Biotechnology as the major subject.

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