

DSM

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Biologics

Bright Science.
Brighter Living.™

Contract Manufacturing &
Technology Solutions

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HEALTH • NUTRITION • MATERIALS





Our purpose is to create brighter lives for people today and generations to come. We connect our unique competencies in life sciences and materials sciences to create solutions that nourish, protect, and improve performance.

DSM is fully aligned with the needs of pharma and biotech, offering committed partnerships that apply our broad technologies, exceptional facilities, and regulatory excellence to the manufacture of customers' products.

Broad diversification and financial strength provide a robust platform for all business units, geared towards sustainability. DSM is focused on growth-oriented positioning in its strategic markets, which ensures it is not only a partner for today, but an intelligent choice for tomorrow.

Biologics

- :: World-class contract manufacturing services and technology solutions for the production of biopharmaceutical drugs
- :: Process development & optimized production based on mammalian cell lines
- :: The strength of a leading company serving the global biotech market

Speed-to-Market

- With so much of the pressure in biopharmaceuticals linked to the time required for development phases, DSM can make a significant difference. The use of many standardized steps and ready-to-use work packages is fine-tuned efficiently by experienced personnel to reduce timelines and
- :: Improve speed-to-market
 - :: Facilitate cost-effective development
 - :: Mitigate financial risk

Regulatory Navigation

Proof of concept is a critical milestone in any biotech project in terms of establishing a good fit in a company's product portfolio and attracting investment and/or acquisition at the earliest possible stage.

DSM's comprehensive customer support and considerable experience with major regulatory agencies helps lead to successful filings. All data and documentation required for cGMP batch material is provided in the required format.



For DSM, quality is a way of life. This is the core of Quality for Life™. Quality for Life™ is the mark of quality, reliability and traceability. It means that DSM customers are getting superior products and services, knowing the source on which they depend. Quality for Life™ means sustainability. It symbolizes our commitment to our environment, consumers, our business partners, our people and the regulatory framework that governs our operations.

With the Quality for Life™ seal, we guarantee peace of mind for you and for your customers.

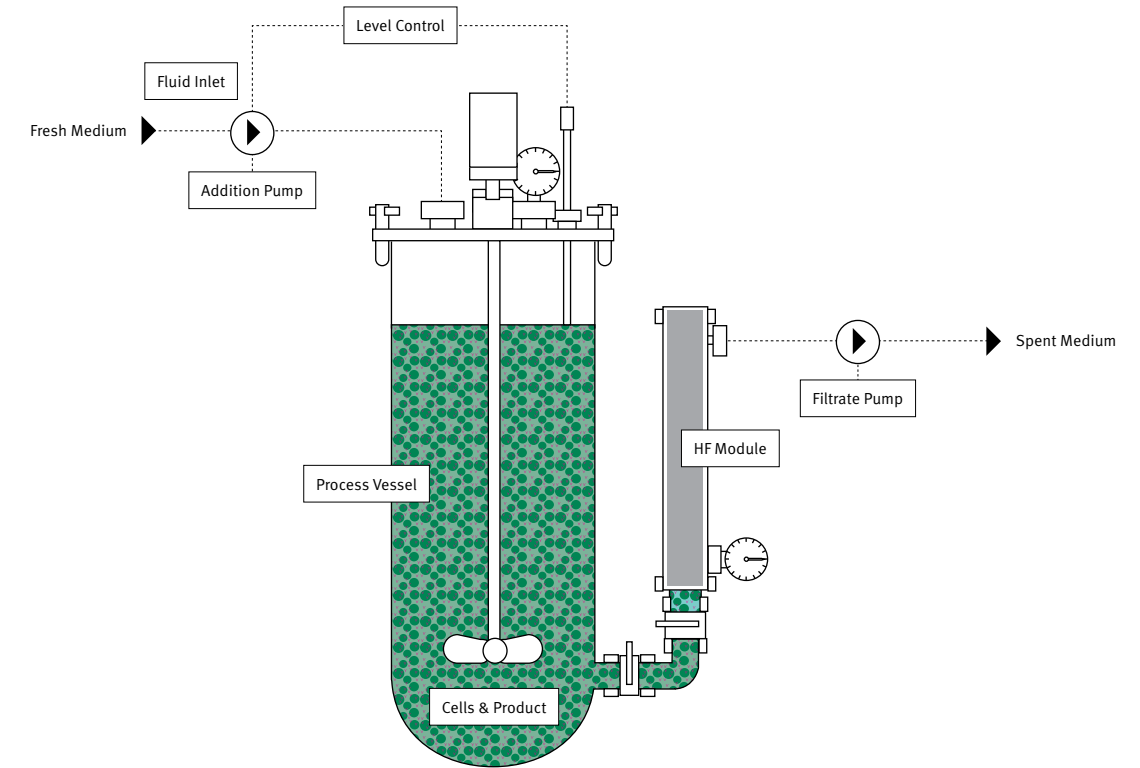
DSM's Proprietary XD[®] Process

A Revolution in Process Technology

How it works

DSM's XD[®] technology works in a continuous media feeding mode, with a filtration unit to retain both cells and proteins of interest in the bioreactor. The constant nutrient supply and wash out of metabolites result in an optimal and constant environment for the cells throughout the batch. Unlike a standard fed batch process the feeding regime is performed with basal media. It's straight forward—no need for a lengthy feed development. The XD[®] process gives greater process control resulting in more consistent quality and lower scale-up risk.

The XD[®] process gives very high cell densities while retaining high cell viability to the end, resulting in very high volumetric productivity with consistent product quality. At the end of the cultivation (~14 days), the complete harvest is processed as one complete batch. The technology has proven suitability for CHO cell lines with 5 to 10 fold yield increases. Cell densities of more than 240 million cells/ml have been achieved independent of the cell line used. This resulted in yields up to 11.5 g/L for recombinant proteins and 27 g/L for antibodies.



The XD[®] benefits

- :: Reduced cost of goods
- :: Commercial manufacturing at smaller scale
- :: Reduced scale-up risk
- :: Consistent product quality
- :: Lower capital expenditure
- :: Compatible with single-use bioreactors
- :: Easy handling

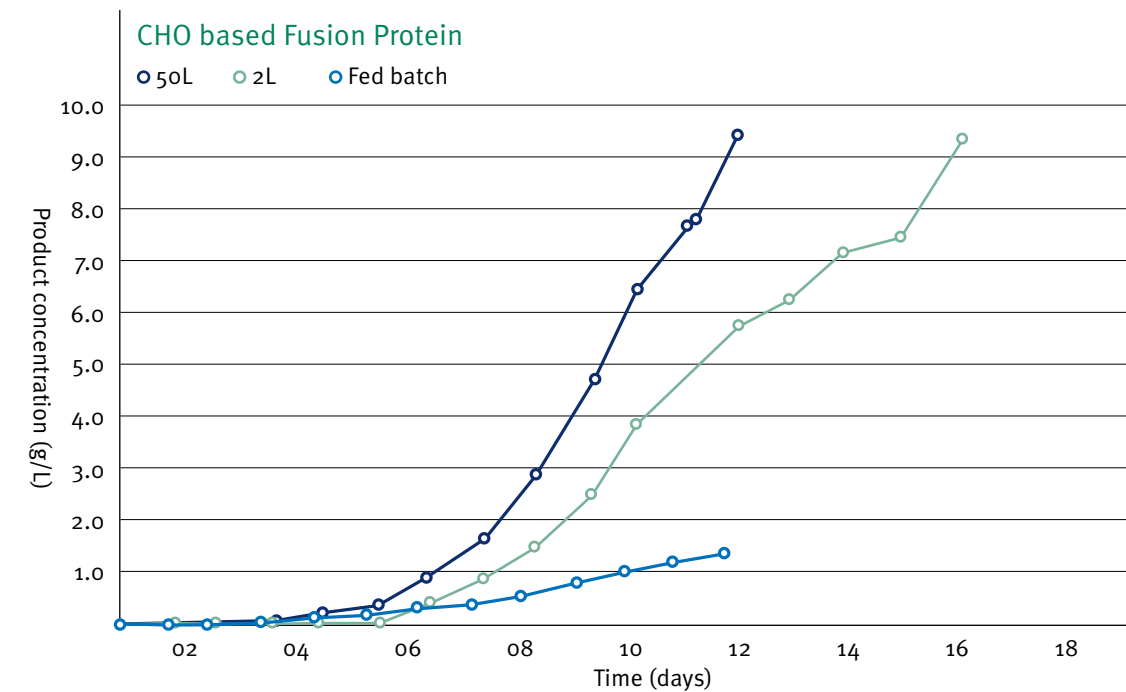
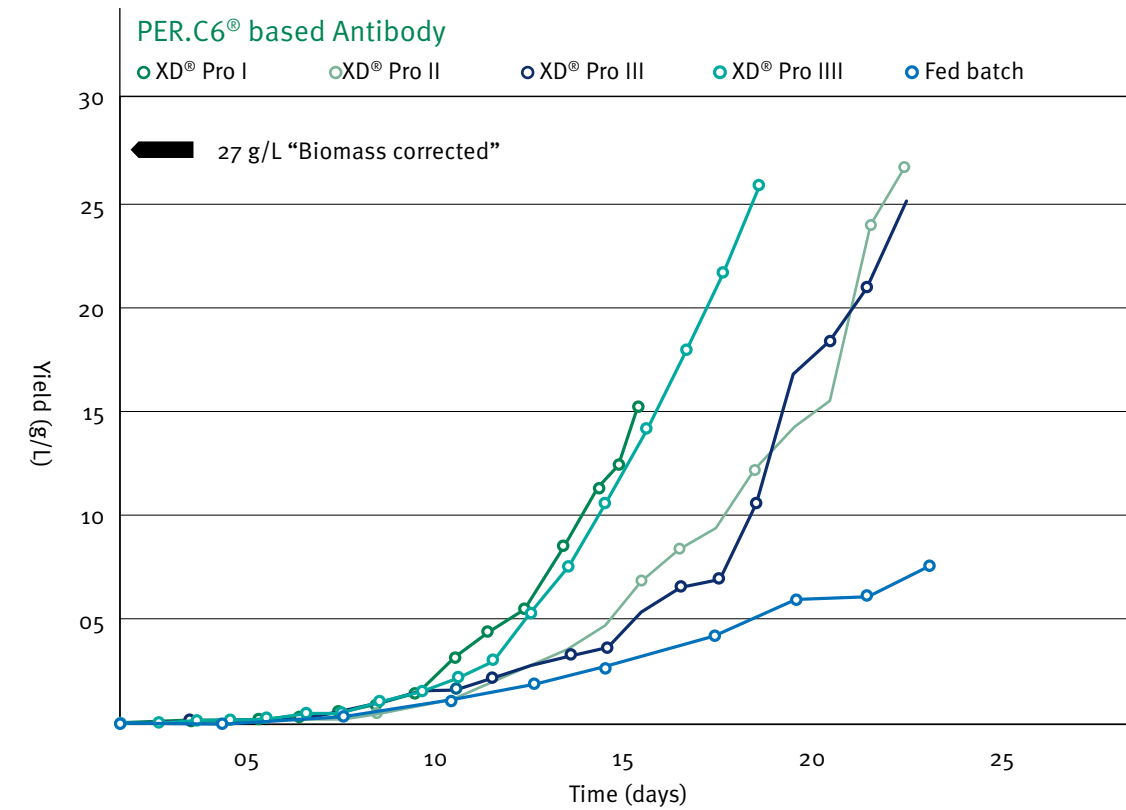
XD[®] with Mammalian Cell Lines

Globally-Favored Expression Platforms

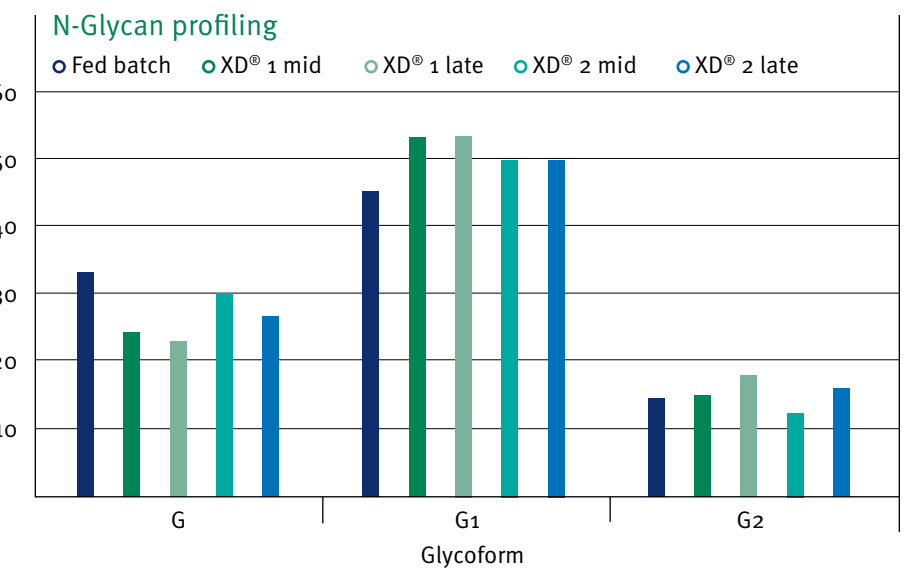
Optimization with XD[®] technology

Mammalian cell lines are still the most widely-used expression platforms for the production of recombinant proteins and monoclonal antibodies. The cost of goods involved in the production of drug substance in mammalian cell lines remains high and solutions are needed. DSM's innovative XD[®] process technology has

driven process yields to new heights— as much as 5 to 10 times higher across different mammalian cell systems. Optimization of these yields provides the opportunity to reduce the cost of goods, minimize scale-up risk, and reduce overall capital expenditure requirements.



XD[®] is a registered trademark of DSM N.V.



Consistent Quality

Comparative analytical studies have shown no differences in product quality from the beginning to the end of an XD[®] run. Unlike typical fed-batch processes, cells are in an optimal metabolic environment throughout the run and therefore consistently produce product of the same quality from beginning to end.

Samples at various points in an XD[®] run are comparable to each other and to a fed-batch-based product in terms of purity, charge heterogeneity, aggregation level, bioactivity and glycosylation profile—as demonstrated in the Glycan profile above. Relatively fewer cellular byproducts are actually present in the final harvest from XD[®] since the cell viability remains very high throughout the run (typically above 95%).

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Contract Manufacturing

Engage a Partner You Can Entirely Trust

DSM offers world-class facilities and expertise to the biopharmaceutical market, providing confidence that quality materials can be produced and delivered in the right quantity on precisely the timeline required.

You can trust DSM's experienced project team for:

- :: Project transparency from the beginning
- :: The focus and flexibility to meet your needs
- :: On-time delivery
- :: Successful realization of your project from concept to completion

Total Value

The cost of developing biotech drugs is determined by a number of factors. DSM understands these and brings total value through approaches that address many of them.

Breakthrough process technologies, such as DSM's proprietary XD® and Rhobust™ process, increase the total value of a biopharmaceutical project for the customer. This results in:

- :: Reduced investment in process development
- :: Reduced investment in material generation for clinical trials
- :: Reduced capital expenditure for newly-designed manufacturing facilities
- :: Reduced scale-up risk
- :: Lower cost of goods

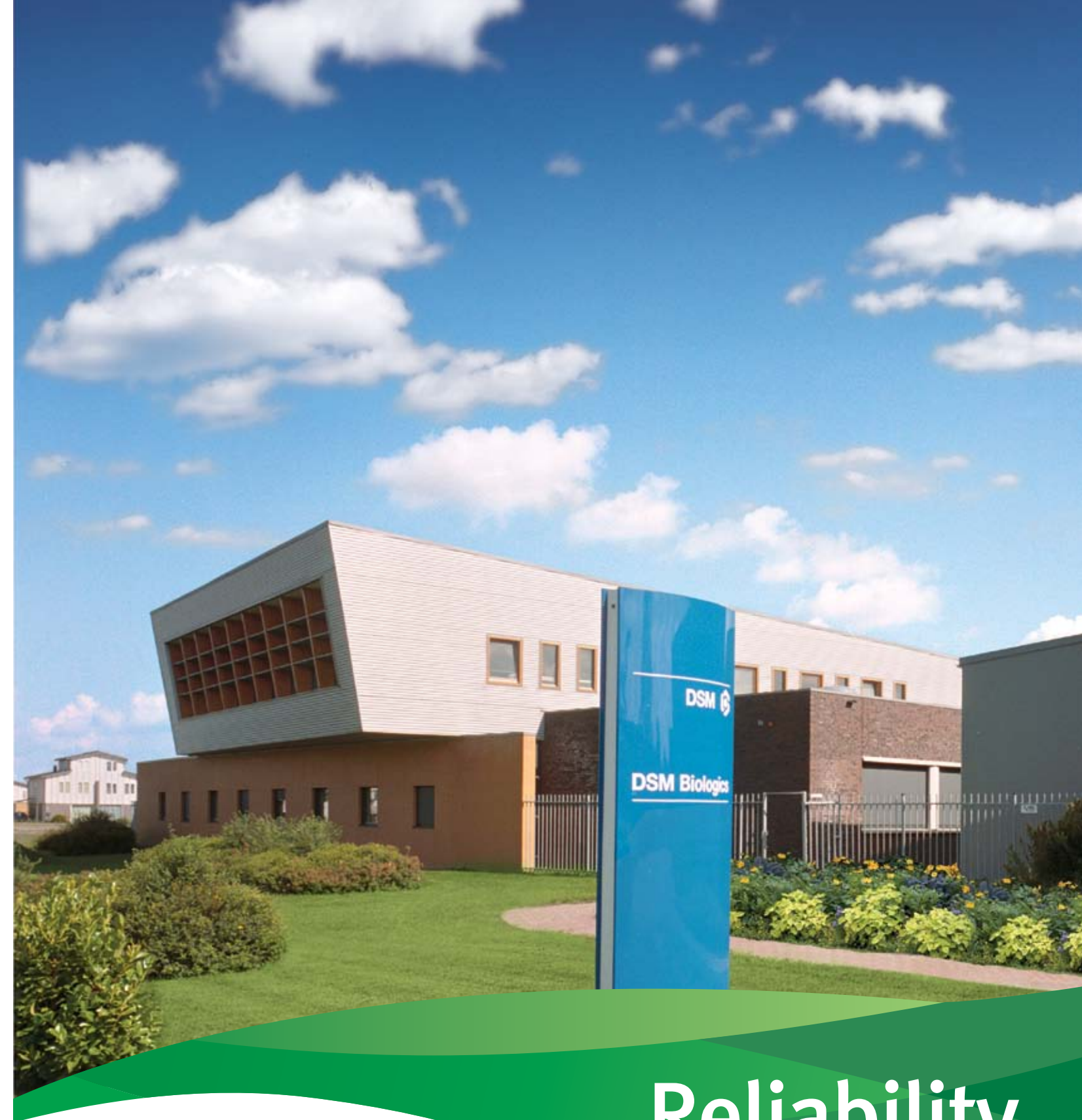
Expression Systems & Process Modes

- :: All commercial cell lines, including CHO cell line
- :: Batch, Fed-batch, Perfusion, XD®
- :: Platform DSP for mAbs, Rhobust™
- :: Scale: 50L, 250L and 1,000L Stainless Steel and Disposable Bioreactors

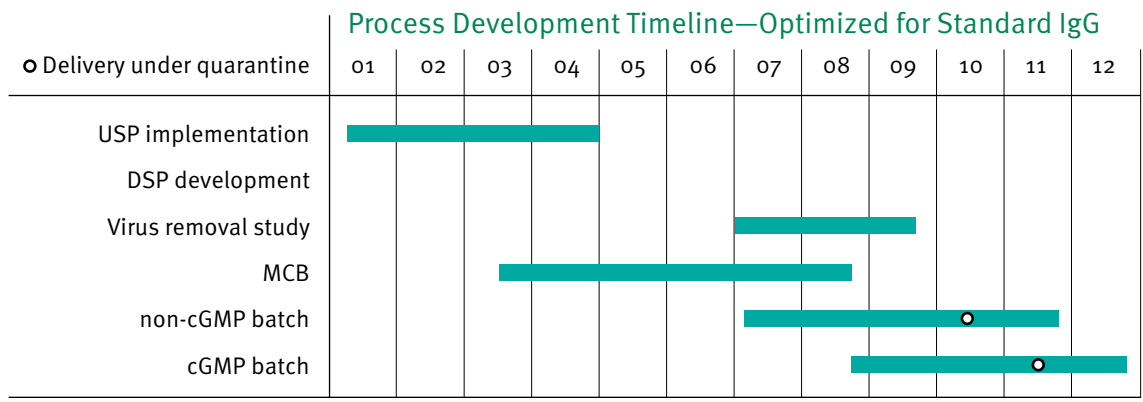
Predictable and Reliable Delivery

The phases of biopharmaceutical drug development and associated clinical trials demand precise coordination of material production and trials. Delays in the availability of material are expensive in terms of the loss of slots at CRO organizations and have a long-term impact. DSM counters this threat by using technologies and processes that increase the degree of predictability, combined with an excellent record for delivering on commitments, so material is available at agreed target dates. This is supported by consistent open communication throughout the project.

XD® is a registered trademark of DSM N.V.



Reliability



Innovation

It's important to know that your CMO is constantly innovating with new technologies. This is a core value at DSM, where the Research and Development team is at the forefront of design of the next generation of bioprocessing technology, which will lower the cost of goods and improve product quality in manufacturing processes.

Project Management

DSM's Project Managers take the lead to ensure that timelines and budgets are met. With broad backgrounds in both development and cGMP, they have the proven skills and experience to get it right the first time.

cGMP Cell Banking

Once a clone has been selected, DSM's Groningen facility performs cGMP Master and Working cell banking with complete characterization and testing services.

Process Development & Scale-Up

Development is a critical part of any program. Going with an experienced team counts when it comes to getting the highest titers, best overall yields, and the right product quality. Starting from a lead candidate cell line, DSM Groningen develops upstream and downstream processes for a project. From the outset, DSM focuses on using standardized process steps and commercially-available raw materials/resins for projects, which help to

reduce the cost of goods and ensure repeatable results for both recombinant proteins and monoclonal antibodies.

After intake of a cell line, the upstream process is developed at a small scale and quickly scaled up to 50 L bioreactor scale in process development labs. Once the initial material is available, the DSP process development begins, according to the properties of the molecule. For monoclonal antibodies, DSM's platform process is adapted to the individual antibody's properties.

Analytical Development

Assays for product identity & process control

- :: HPLC
- :: Immunological Assays
- :: Colorimetric Assays
- :: MS
 - :: Capillary Electrophoreses
 - :: DNA assays
 - :: Others in cooperation with external partners

USP Development

Grams for identity & formulation studies

- :: Cell lines
- :: CHO, Per.C6, ...
- :: Media Optimization
- :: Process Development
- :: Batch
- :: Fed-batch
- :: Perfusion
- :: XD®

DSP Development

Materials for tox & stability studies

- :: Concentration Steps
- :: Rhobust™ (Expanded Bed Adsorption)
- :: Dead end filtration
- :: Cross-flow filtration
- :: Chromatography Development
- :: Protein A
 - :: Hydrophobic interaction
 - :: Ion exchange
 - :: Size exclusion
 - :: Virus Filtration
- :: Final Product Concentration

Clinical Supply

Materials for tox & stability studies

- :: Transfer documentation to cGMP facility
- :: Pilot batch
- :: cGMP manufacturing
- :: Delivery to fill & finish site

Commercial Supply

Material to your demand

- :: Phase III
- :: Commercial
- :: Up to 1,000L
- :: High yield process XD®
- :: Downstream optimization
- :: Rhobust™ (Expanded Bed Adsorption)

Regulatory Support

cGMP process & filing documents

- :: MCB
- :: Stability studies
- :: Process validation
- :: Virus validation
- :: Assay validation
- :: Support for CMC section

cGMP Manufacturing

Once the process has been scaled up in process development labs, tech transfer to the DSM cGMP facility takes place according to well-developed and time-tested SOPs (Standard Operation Procedures). Cross functional teams from development and manufacturing groups are assigned to ensure a smooth transfer. The DSM Groningen facility was intentionally designed with much of the same equipment in both development and cGMP areas to reduce transfer risk and ensure repeatable results during scale-up to cGMP.

Analytics, Stability Studies, Validation Services & Regulatory Support

DSM has a full range of analytical development capabilities to help identify and characterize a recombinant protein or antibody. For cGMP work, DSM will qualify and/or validate all relevant assays needed for in-process and final release testing. As a project approaches later clinical phases, DSM offers full assay validation services. DSM supports regulatory filings with full capabilities to perform stability studies for both drug substance and drug product at a range of different temperatures. The manufacturing-related section (CMC section) is also provided in the right format (CTD).

Validation

Once a project reaches the clinical trial phase II, DSM provides the full validation package needed for clinical phase III and commercial market supply. This includes a full validation of the analytical assays, complete virus validation of the DSP process according to current guidelines, and process validation including process critical parameters, consistency series and the relevant CMC section documentation.

PER.C6® is a registered trademark of Crucell Holland B.V. XD® is a registered trademark of DSM N.V.



Groningen, The Netherlands

DSM Groningen

Located less than two hours by car or train from Amsterdam International Airport in The Netherlands, DSM Groningen is a world-class facility dedicated to the development, scale-up, and cGMP manufacturing of recombinant proteins and antibodies. Experience counts, and with over 25 years of contract manufacturing know-how and a range of cGMP capacities—DSM has the right people, the right equipment and the right skills to deliver high quality projects on time and on budget.

Facility Details

- :: Area: Process development: ~20,000 sq ft / cGMP: ~20,000 sq ft
- :: Reactor: 3 flexible suites with 50/250 L reactors and single-use flexible suite for 1,000L scale
- :: DSP: Several suites pre-/post-virus removal equipped with filtration devices, dead-end, cross-flow filtration (micro-, ultra-, nano-filtration), Rhobust™ (Expanded Bed Adsorption)
- :: Chromatography: Affinity-, Cation-, Anion-, Size-exclusion chromatography (resins or membrane processes)
- :: Virus removal: pH-, solvent treatment, filtration
- :: Filling: Filling of substance in transport containers

Commercial Supply

Once a product reaches clinical phase III, DSM provides support through to approval for market supply. The Groningen facility has consistently been successful when inspected by regulatory bodies.

Quality

DSM's Quality Assurance team sets the standard when it comes to compliance. With a stellar inspection history spanning more than 25 years, the DSM Groningen team adheres to the highest standards in the biopharmaceutical industry. With inspections from all major US and European agencies, you can be assured you are getting the best.

Technology Solutions

Making Next Generation Manufacturing Leaner and Efficient

Premium Technology

DSM's unique position in being able to license superior process technologies, like the proprietary XD[®], makes the business a sought-after technology provider. For newly-designed manufacturing facilities, these technologies have the potential to condense the manufacturing footprint and reduce capital investment, which will achieve a lower cost of goods relative to standard large-scale manufacturing.

XD[®] Technology DSM's proprietary XD[®] technology optimizes mammalian yields by increasing the cell density within a bioreactor and boosting output by 5 to 10 times, when compared to a fed- batch process. Yields as high as 27 g/L for antibodies are possible, with cell densities reaching 240 million cells/ml.

In combination with disposable equipment, this leads to a smaller footprint and reduced capital investment for commercial manufacturing facilities. Competitive cost of goods relative to a standard large-scale biopharmaceutical plant is achievable with a 1,000L disposable bioreactor.

Rhobust™ Technology is the next generation expanded bed chromatography (EBA), using cross linked agarose beads with Tungsten Carbide to increase the particle density. Rhobust™ is applied as one single harvest step for capturing high-value active proteins in a pure concentrated form.

Rhobust™ Technology

Downstream Optimization Process for Direct Product Capture

Performance

Rhobust™ technology allows process intensification by integrating clarification and product capture into one single step. Crude, high cell density or highly viscous and particulate feed streams can be loaded directly on the column. Cells and/or debris flow through the expanded bed unharmed and the product is bound. By acting as a direct capture for mammalian and microbial harvest, Rhobust™ reduces processing time and assures lower costs without affecting product quality.

A Beneficial Match

The Rhobust™ technology combines especially well with high titer, high cell density harvests such as DSM's proprietary XD[®] process. As a platform approach to significantly improve bioreactor output for mammalian cell culture, the XD[®] process technology constantly delivers product titers higher than 10 g/L and cell densities above 100 million cells/mL, which are not easily removed by depth filtration or centrifugation. The Rhobust™ system copes very well with high cell density harvests, allowing efficient product capture and cell

removal in only one step. When used in combination, DSM's proprietary XD[®] and Rhobust™ technologies enable biopharmaceuticals to be processed at significantly reduced time and costs and ensure high quality achievement when compared to standard upstream and downstream technologies.



Technology Solutions

Making next generation manufacturing leaner and efficient

Premium Technology

DSM Biologics' unique position in being able to license high-yielding expression platforms in combination with superior process technologies, like the proprietary XD[®] process, makes the business a sought-after technology provider. For newly-designed manufacturing facilities, these technologies have the potential to condense the manufacturing footprint and reduce capital investment, which will achieve a lower cost of goods relative to standard large-scale manufacturing.

XD[®] Technology

DSM's proprietary XD[®] technology optimizes mammalian yields by increasing the cell density within a bioreactor and boosting output by three to five times, when compared to a fed-batch process. Yields as high as 27 g/L for antibodies are possible, with cell densities reaching 180 million cells/ml. In combination with disposable equipment, this leads to a smaller footprint and reduced capital investment for commercial manufacturing facilities. Competitive cost of goods relative to a standard large-scale biopharmaceutical plant is achievable with a 1,000L disposable bioreactor.



The Quality for Life™ commitment.

...gives you "Peace of Mind"

- ∴ It is the mark of product—*quality, reliability & traceability*
- ∴ It means you are getting the very *best ingredients*
- ∴ You know *where the ingredients come from* and you know you can *rely on this source*

...means *Sustainability*

- ∴ It symbolizes *our commitment* to our environment, our business partners, our people and the regulatory framework that governs our operation