Benchling

for Industrial Biotech R&D

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Industrial biotechnology is transforming traditional manufacturing technologies by providing more eco-friendly approaches like bioprocessing and biomanufacturing. Industrial biotech has a wide range of applications — agriculture, beverages, biofuels, chemicals, consumer goods, foods, industrial enzymes, materials, microbial technologies, therapeutics, and more. The list of applications for industrial biotechnology continues to grow. However, there are several hurdles for industrial biotech companies seeking to develop next-gen strains, novel processes, and new applications.

Industrial Biotech Research

Library Screen
- Library selection
- NGS screen

Literature Mine
- Genes of interest
- Target sequencing

Strain Creation
- Sequence design
- Cloning

Primary Screens
- Strain growth assays
- Plasmid expression
- Activity assays

Process Development
- Strain scale-up
- Compound production

Analytical Assays
- Purity, yield and potency assays

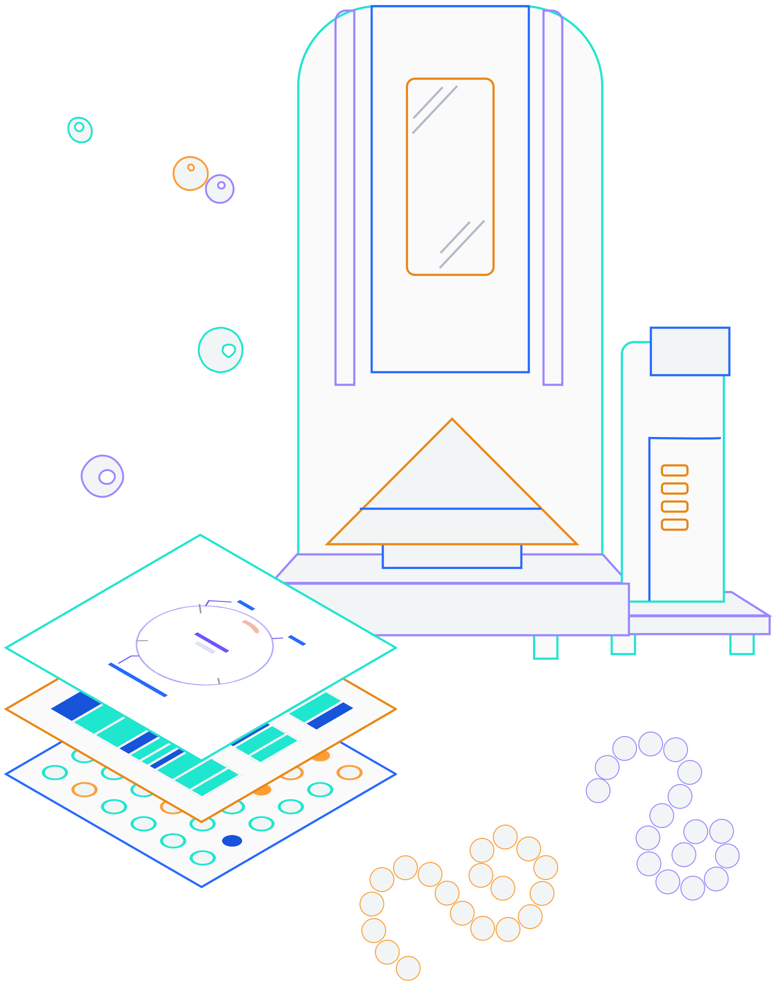
Industrial Biotech Development

Fermentation
- Strain scale-up

Strain QC
- Strain concentration
- Metabolite measurements

Compound Purification
- Separation from strain
- Purification

Compound QC
- Identification assays
- Compound measurements



Complexities in Industrial Biotech Research

- Increasing diversity of industrial biotech research and its applications means that labs need to **manage a wide range of biological components** — from proprietary DNA parts to microbial chassis — while computing and documenting their properties at the sequence level
- Constantly evolving techniques make it challenging to **handle multi-step processes**, including designing custom sequences, inserting them into chassis, and characterizing these systems with unique functional assays
- Rational engineering of microbial systems requires the **integration of omics-assisted approaches** for characterizing and modeling

Complexities in Industrial Biotech Development

- Creating standardized and scalable fermentation processes requires development teams to **overcome scale-up and process development challenges**, identify relevant process parameters, and link process with strain performance characteristics
- Thoroughly understanding strain performance and by-product characteristics means that companies need to **consolidate results from an analytical core** throughout process development and production
- Improving biomanufacturing efficiency requires teams to **integrate with automation**, simplify upstream and downstream processes, and centralize accompanying data and analytics in a single platform

> This paper outlines the critical needs and complexities of industrial biotech R&D, and how Benchling has helped address these challenges for leading industrial biotech companies

Industrial Biotech Research

Industrial biotech research takes advantage of innovative science and cutting-edge techniques to identify strains and enzymes that have promising properties and novel by-products. Here are some of the key research complexities and needs that define industrial biotech research.

1

Managing a wide range of biological components used and clearly documenting their properties

Why is it a critical need?

Industrial biotech labs designing custom sequences manage a variety of entities. These include cell factory chassis — bacteria (e.g., E. coli and C. glutamicum), yeast (e.g., S. cerevisiae), and cell lines (e.g., CHO cells and Taxus plant cells) — and libraries of proprietary DNA parts (e.g., regulators, promoters, terminators, and repressors). Additionally, teams need to calculate theoretical properties of engineered sequences and record relevant properties, many of which vary from entity to entity. Because the engineered sequences and their unique attributes are often the basis for intellectual property, this is of utmost importance to industrial biotech research teams.

Why do current solutions fail?

Current solutions simply lack the flexibility to manage such a diverse range of entities on a single solution. Scientists often rely on a combination of disparate tools from specialized registries to spreadsheets. Moreover, their registration system is often different from the system that manages their sequence files. The fragmentation of registry systems and sequence files makes capturing corresponding results cumbersome. Consequently, discovery of information also becomes difficult.

How Benchling helps

Benchling's comprehensive platform includes a Molecular Biology application to design novel engineered strains, a Registry application to build a library of custom entities and DNA parts, and an Inventory application to track the physical locations of samples.

Design and develop engineered strains in batches with Molecular Biology such as Bulk DNA Assembly

- Use the Bulk Assembly Wizard to create multiple test biotic prototypes at once
- Perform bulk cloning, bulk annotation, and bulk translation of plasmids and other DNA sequences

Create a registry of all your strains and constructs with customizable data modeling and sequence-level intelligence

- Build a single database for all of your microbial chassis, enzymes, and proprietary DNA parts
- Automatically compute attributes of novel DNA constructs based on sequence-level algorithms and capture relevant properties in fully customizable schema fields

Link physical inventory to your registered entries

- Link batches in containers and freezers to the entries in the registry
- Integrate with plate readers, smart fridges, barcode scanners, and printers to further streamline management of your strain and enzyme inventory

2

Handling complicated multi-step processes to construct and characterize biological systems

Why is it a critical need?

Once DNA parts are assembled and tested in silico with computer-aided design, a series of processes are required to construct sequences, test sequences for function, and ultimately insert DNA sequences into the chassis. The sequences are typically packaged into vector scaffolds such as plasmids or viral phagemids for delivery to the target cell or chassis. The vectors are delivered to the cells or chassis with transfection methods such as electroporation, cationic lipids, or viral transduction. These methods are complex, and are constantly evolving with the field. Industrial biotech research organizations need a flexible workflow system that can keep up with constantly changing processes, mapping and managing sample hand-offs, inputs, outputs, and variations of the steps in each process.

Why do current solutions fail?

Because industrial biotech processes are new and evolving, standardized management solutions are lacking. In cases where processes are complicated, customized LIMS are often used to manage samples and results. But when processes need change, these same LIMS systems are difficult to update. Often, coding is required to reconfigure the systems. In situations with less complicated processes, scientists rely heavily on unstructured tools such as spreadsheets or text documents. Software tools built to effectively manage industrial biotech's complicated and quickly changing processes are almost nonexistent.

How Benchling helps

Benchling's fully configurable Workflows application simplifies and standardizes the complex series of steps used in the assembly, testing, and generation of novel biological systems.

Create custom workflows to suit systems biology, synthetic biology, or directed evolution applications

- Easily map entire, multi-step processes from the construction of sequences to insertion into microbial chassis
- Manage multiple standardized processes for creating and testing DNA sequences and engineered strains simultaneously

Flexibly edit workflows as engineering strategies change

- Use Benchling's point-and-click user interface to make changes to workflows without coding
- Create branching studies to test multiple sequences under varying conditions

Trace engineering workflows, strains, and corresponding products

- Visualize your entire process end-to-end and trace sample lineage from start to finish
- Track progress in real-time and access supporting experimental Notebook entries directly

3

Integrating with omics-assisted approaches to support rational engineering

Why is it a critical need?

Rational engineering is the informed design of custom cell factories, aided by computational models and omics-based characterization data. In rational engineering, the natural activity of an existing cell or enzyme is altered through the selection of mutations. Multi-omics-based approaches help in understanding the mechanisms and pathways involved in the production of the target end product. These data, along with computational modelling, are used to help select mutants with desirable attributes. Omics-based approaches include genomics, transcriptomics, proteomics, metabolomics, and fluxomics, which all produce massive amounts of data. Research teams need to integrate and analyze large omics-based datasets for effective in silico modeling and rational engineering of microbial systems.

Why do current solutions fail?

Current solutions are fragmented. Each omics-based approach uses its own custom software to capture and process data. The software used for in silico modeling and screening are also distinct from omics software. This siloed software ecosystem leads to cumbersome handling and merging of datasets, and it increases the risk of errors in data processing and interpretation.

How Benchling helps

Benchling's cutting-edge developer platform helps manage all omics-related results and provides the software foundation for developing engineered strains with superior performance characteristics.

Integrate genomics, transcriptomics, proteomics, metabolomics, and fluxomics data

- Capture results from different omics-based approaches in a central SQL Data Warehouse
- Automatically upload results from your bioinformatics pipeline using Benchling's REST APIs

Combine characterization results to improve in-silico modeling approaches

- Run custom queries on the Benchling SQL Data Warehouse to gain a comprehensive understanding of your characterization results
- Integrate in silico tools to query or read results directly from the Benchling Developer Platform

Track iterative improvements in strain function and substrate generation

- Build custom dashboards to monitor real-time improvements in strain performance with each iteration
- Hook Benchling up with visualization tools such as Tableau and Spotfire to view historical trends

Industrial biotech development involves developing reproducible and well-controlled fermentation processes that ensure a high quality final product with good yield. Here are some of the key development complexities and needs that define industrial biotech development.

1

Overcoming scale-up and process development challenges

Why is it a critical need?

Developing strains that maintain their desired production characteristics during large-scale fermentation is challenging. There are several factors that contribute to this complexity. First, low titers and yields need to be overcome in the laboratory setting before teams can proceed with scale-up. Second, the environment of commercial-scale bioreactors is drastically different from that of laboratory-scale plates or shake flasks. Third, predicting strain performance in industrial-scale bioreactors is difficult because of fluctuating bioreactor conditions, genotypic drift during long-term cultivation, and other physiological considerations. During process development, organizations need to identify relevant processes, parameters, and analytics that help them design strains with ideal scale-up characteristics.

Why do current solutions fail?

A set of disparate software tools are used in the process development setting. Software for controlling and collecting data from bioreactors is different from the software used for data analysis. Additionally, unstructured tools such as spreadsheets and text documents are frequently used to handle sample information, results, and basic analytics. This leads to inefficient processes and data silos.

How Benchling helps

Benchling addresses the critical challenges of scale-up and process development by providing Notebook, Workflow, and Registry applications that work in tandem to help you design, execute, document, and share process development studies on a single platform.

Design fermentation process development studies

- Perform several scale-up studies simultaneously to identify relevant parameters and stresses from thermal, mechanical, and chemical sources
- Use laboratory-scale results and high-throughput results to inform the design of process development studies

Map the entire production process on a single platform

- Visually outline all of the steps in the production process including stages, inputs, and outputs
- Create and adjust processes to accommodate variability in strain performance and process characteristics across multiple runs

Create and share standardized processes for scale-up

- Use workflow templates to organize and standardize steps in your production process as it is finalized
- Collaborate with manufacturing tech transfer teams seamlessly, sharing the final processes

2

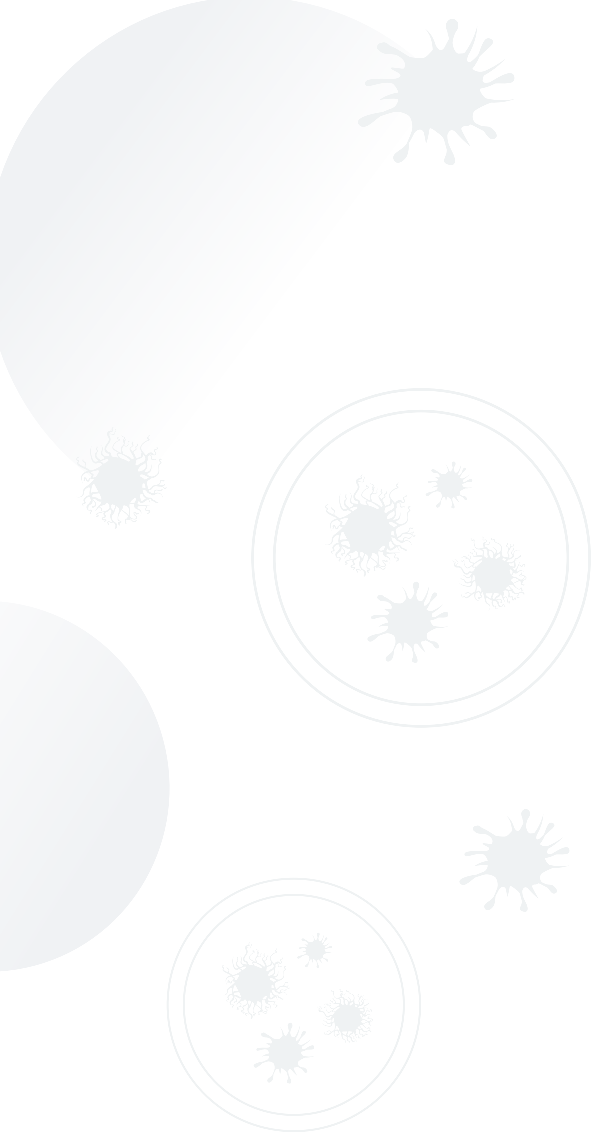
Consolidating results from analytical core throughout production

Why is it a critical need?

Analytical characterization is integral to development and manufacturing. The analytical core within an R&D organization studies several types of samples — from the starting materials, in-process samples, and substrates to the final product. Their work ensures that the process is performing as designed, verifying that the intermediate and final output from each unit operation is exactly as desired. Analytical characterization can be performed either online or offline. Online measurements require integration of manufacturing equipment with process analytical tools (PAT). Offline measurements require the coordination of sample submission and reporting back of results in a timely manner. Industrial biotech development teams need to create a central repository of all characterization results and streamline their communication with other functions.

Why do current solutions fail?

Scientists currently use software systems that are highly fragmented and do not mirror their experimental steps or their handoffs. The software tools used by the analytical core are different from those used by the process development or manufacturing teams. For example, specialized software controls and captures data from analytical instruments, spreadsheets help to analyze the results obtained, e-mails help to coordinate the sample hand-offs, and text documents help to document the results. This leads to inefficient sample hand-offs, unstructured results, and poor communication.



How Benchling helps

Benchling's Requests, Registry, and Developer Platform integrate the analytical core with process development and manufacturing teams by providing a single platform to coordinate request generation, analytical results generation, and delivery of results in a timely and efficient manner.

Integrate with cutting-edge instruments and analytical tools to model complex assays

- Connect analytical instruments directly to Benchling to create a central hub for all characterization results
- Interface with online measurement tools for in-process characterization of your samples

Link strain performance to characteristics of by-products such as metabolites and enzymes

- Thoroughly study the characteristics of starting materials, substrates, intermediates, and products and link results to corresponding batches in the Registry
- Measure strain performance properties such as titer and yields against specific steps in the production process

Establish a continuous feedback loop between process development, production, and analytical teams

- Streamline every step of request management for comprehensive characterization of starting material, in-process samples, and final product
- Use the @-mentioning feature to notify key stakeholders across process development and production as soon as new data becomes available

3

Integrating with automation to improve efficiency of biomanufacturing

Why is it a critical need?

Biomanufacturing processes for microbial strains are well established; techniques such as fermentation have been in use for decades. However, the extension of this knowledge to novel organisms that haven't been routinely cultured at the manufacturing scale poses several challenges. Because manufacturing engineered strains can be expensive and resource intensive, it is important to make the manufacturing process as automated and streamlined as possible. Industrial biotech organizations need tools that help them automate and streamline their processes to ensure that products are produced with the desired quality, with the optimal yield, and at a low cost.

Why do current solutions fail?

The use of software in manufacturing is either inconsistent or nonexistent. Most recordkeeping is done in the form of paper-based forms and notebooks. In cases where manufacturing automation is used, specialized software is used to control manufacturing equipment. These systems are often distinct from LIMS systems that might be used to collect and store raw data. This incoherent use of software leads to inefficient manufacturing processes, cumbersome data collection, and redundant results analysis.

How Benchling helps

Benchling streamlines biomanufacturing by providing an easy to use Workflows application, a developer platform for integrating with automation, and a unified software platform for centralizing upstream and downstream processes.

Access complete process development history

- View all results from previous process development studies in one place to set up biomanufacturing effectively
- Review the history of a process by accessing previous versions of the workflow

Automate data capture from bioreactors to effectively monitor fermentation

- Connect with bioreactors of varying scale to automate data capture, centralize results, and access process parameters on a single platform
- Build dashboards to monitor in-process fermentation parameters, such as temperature, oxygen gradient, CO2, and glucose

Centralize upstream and downstream biomanufacturing processes

- Connect production equipment from both upstream and downstream processes on a single platform
- Run complex queries on data stored in the SQL Data Warehouse to analyze historical trends in process output (e.g., yield and purity) and biomanufacturing efficiency

Conclusions

Industrial biotech is expected to have a major impact on several industries, including healthcare, food and beverages, materials, and sustainable energy. The technologies and processes supporting the discovery and development of novel strains are evolving rapidly as new applications are identified.

Benchling provides a modern, fully configurable, and user-friendly platform that adapts to the rapidly evolving needs of industrial biotech R&D. This enables organizations to accelerate industrial biotech R&D and bring their innovative products to the market more efficiently.

Here are some companies that use Benchling for industrial biotech R&D:

Bolt Threads
zymergen
AgBiome
Antheia
ASIMOV
eligo bioscience
enEvolv
FINCH
Hexagon Bio
LUMEN BIOSCIENCE
SENTI BIO
synlogic
Synpromics the leader in gene control

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