



Genes to GMP: How Biocatalysis Accelerates the Development of New Medicines

Biocatalysis has emerged as a transformative technology in Active Pharmaceutical Ingredient (API) development, reshaping how pharmaceutical molecules are developed and manufactured. By enabling shorter synthetic routes, improved chemo-, regio- and stereoselectivity, and more sustainable manufacturing processes, enzymes are increasingly outperforming traditional chemical catalysts. Over the past two decades, advances in enzyme discovery, screening and engineering have dramatically reduced the cost and time required to access new biocatalytic activities, making enzymes increasingly attractive alternatives to traditional chemical catalysts.

The growing adoption of biocatalysis within pharmaceutical development has been driven not only by advances in enzyme technology, but also by the emergence of integrated development models that combine enzyme discovery, engineering and AI, process development/optimisation and manufacturing. Access to diverse enzyme libraries and effective screening platforms remains critical, particularly when development timelines are compressed. At the same time, the ability to rapidly scale successful biocatalytic transformations from laboratory evaluation to GMP manufacture has become an increasingly important differentiator. Within this environment, organisations that combine biological and chemical process expertise are well positioned to accelerate the development of efficient and commercially viable manufacturing routes. At Almac, these capabilities are integrated within a single development and manufacturing framework, allowing biocatalytic solutions to be efficiently advanced from early-stage development through to commercial production.

Initially, API development focuses on speed and selectivity, typically using commercially available enzymes and batch processing to quickly identify viable biotransformations to deliver material fast. As the API progresses through its lifecycle and the API process matures, the emphasis shifts towards yield and productivity, driven by the introduction of engineered enzymes and process optimisation. This progression enables robust, scalable and economically competitive manufacturing processes suitable for commercial API production and is summarised in Figure 1.¹

Almac established its dedicated biocatalysis capability in 2005 with the creation of an in-house molecular biology team focused on recombinant enzyme production. This capability removed reliance on third-party enzyme suppliers and enabled direct integration of biocatalysis into chemical process development and GMP manufacturing. Since then, Almac has built an extensive portfolio of proprietary enzyme libraries designed to operate under industrially relevant process conditions and support a broad range of pharmaceutical transformations. Importantly, these capabilities are closely linked to chemical

process development and scale-up expertise, allowing successful biocatalytic reactions to progress seamlessly from enzyme identification and proof-of-concept studies to GMP production campaigns conducted at scales from 20 L to 8,000 L.

This strong track record in the successful scale-up and commercialisation of biocatalytic processes across all six major enzyme families has enabled Almac to deliver robust manufacturing solutions from early development through to commercial GMP production. The breadth of experience in the last 8-10 years, encompassing over 100 route scouting, GMP manufacturing and enzyme supply programmes, demonstrates Almac's capability to identify, develop and industrialise biocatalytic transformations that enhance process efficiency, product quality, sustainability and overall manufacturing economics.²

Carbonyl reductases represent the most widely deployed enzyme class, with >55 manufacturing projects and enzyme supply programmes, reflecting the growing demand for highly selective ketone reductions in pharmaceutical synthesis. Significant activity has also been delivered using lipases and esterases (>20), supporting esterification, hydrolysis and kinetic resolution chemistries. Other frequently applied enzyme platforms include amino acid dehydrogenases, imine reductases, transaminases and Baeyer-Villiger monooxygenases (BVMOs), enabling the efficient synthesis of chiral intermediates and complex APIs.

Beyond these established enzyme classes, Almac has successfully implemented more specialised biocatalysts, including lipoxygenases and P450 hydroxylases, demonstrating the capability to develop and scale challenging oxidation and functionalisation reactions, including development of the chemical engineering aspects of these programmes.

The introduction of structure-guided enzyme engineering has revolutionised how enzymes are engineered quickly and cheaply. Rather than relying on large-scale random

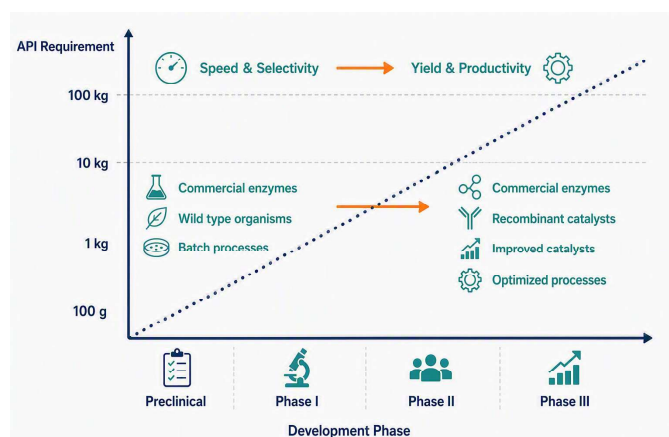


Figure 1: The speed vs cost paradigm shift during drug development

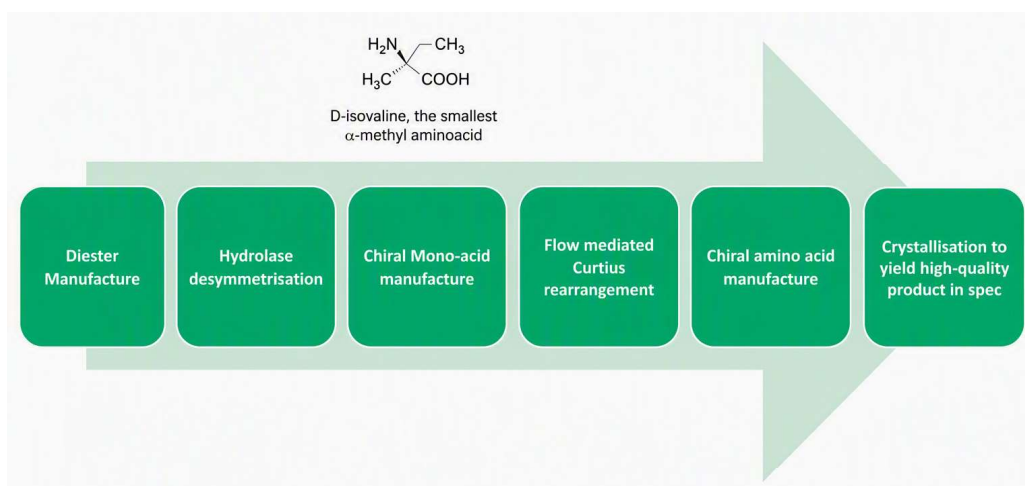


Figure 2: Example process to α -alkylated amino acids

mutagenesis campaigns, Almac has developed a rational design strategy that combines computational modelling with focused experimental screening. This approach delivers a much higher proportion of beneficial variants and enables the tailoring of enzymes to improve activity, selectivity, stability and manufacturing economics. Of the many problems solved via rational mutagenesis, two recent examples concern the large scale biocatalytic synthesis of (R)-2-Methoxymandelic acid, a pharmaceutical intermediate, and the development of a low cost bioreduction route to essential medicines Etonogestrel and Norgestrel on behalf of the Gates Foundation as published in peer-reviewed journals.³

Biocatalysis should be considered as a component within a broader technology platform. For example, in many cases it is deployed hand in hand with flow chemistry, physical sciences and radiolabelling capabilities. The integration of these disciplines enables the development of efficient end-to-end manufacturing solutions.

One recent example within the Almac portfolio of projects included development of a platform technology for α -substituted amino acids, important building blocks for next-generation peptide therapeutics. Biocatalytic desymmetrisation, continuous flow processing and crystallisation science are used to deliver scalable routes to these high-value intermediates while maintaining control of product quality and manufacturability. Figure 2 shows an example manufacturing process to one of the simplest amino acids, D-isovaline.

Biocatalytic Assembly of Oligonucleotides

One of the most exciting areas for biocatalysis is the rapidly growing oligonucleotide therapeutics sector. Oligonucleotides, including siRNA, antisense oligonucleotides and other RNA-based medicines, are becoming increasingly important treatment modalities for a wide range of diseases. As the complexity and demand for these molecules continue to increase, so too does the need for more efficient and scalable manufacturing approaches.

For decades, oligonucleotides have been produced primarily through solid-phase synthesis (SPS), a process involving successive cycles of deprotection and coupling reactions to assemble an oligonucleotide one nucleotide at a time. While highly effective for many applications, the approach becomes increasingly challenging as sequence length and structural

complexity increase. Small inefficiencies at each coupling step accumulate throughout the synthesis, leading to reduced overall yields and increased impurity profiles. The resulting purification burden can become one of the most significant contributors to manufacturing cost, particularly for longer RNA sequences.

To address these challenges, significant research activity across the industry is now focused on enzymatic and hybrid manufacturing approaches. Biocatalytic methods offer the potential to leverage the inherent sequence recognition capabilities of enzymes to improve selectivity, reduce impurity formation and simplify downstream processing.

One promising approach is the use of RNA ligase enzymes to assemble oligonucleotides from shorter pre-prepared fragments, often referred to as blockmers. Rather than building the molecule one nucleotide at a time, larger sections of the oligonucleotide are joined together through enzymatic ligation. By exploiting complementary strand templating, RNA ligases can selectively couple the correct blockmers while rejecting many sequence-related impurities, resulting in improved product quality and reduced purification requirements.⁴ At Almac, we deploy the 3:2:3 approach as shown in Figure 3. This figure illustrates a 3:2:3 iterative assembly strategy for the synthesis of complex oligonucleotides. In each cycle, three blocks are initially present, annealing through base-pair recognition (Step 1). An enzymatic ligation reaction then joins the two annealed blocks, generating a new, larger fragment, reducing the reactor contents from three blocks to two. An in-process control (IPC) is performed to confirm complete conversion of the starting materials. Once conversion is

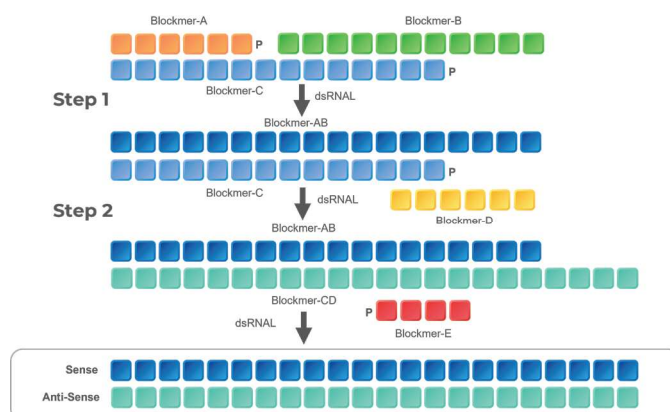


Figure 3: How shorter blockmers are assembled.



verified, a new building block is charged to the reactor, returning the system to three blocks and initiating the next assembly cycle. This sequence of annealing, ligation, IPC verification and block addition is repeated until the full-length oligonucleotide API has been assembled, providing a controlled, modular and highly efficient manufacturing process.

Development of RNA ligase technology has demonstrated the potential of this approach for manufacture of both single-stranded and double-stranded RNA targets right through to GMP materials use in human clinical trials. Continued advances in enzyme discovery and rational protein engineering have improved enzyme stability, activity and tolerance towards modified nucleotides, helping to expand the range of oligonucleotide structures that can be manufactured using enzymatic assembly strategies.

While solid-phase synthesis is expected to remain an important manufacturing technology for many years, enzymatic ligation approaches represent a promising complementary platform. As enzyme performance continues to improve, biocatalytic assembly has the potential to support more efficient and sustainable manufacture of increasingly complex oligonucleotide therapeutics, helping the industry address future demands for scale, quality and cost-effective production.

As biocatalysis continues to expand beyond laboratory-scale applications, the development of robust enzyme manufacturing processes has become increasingly important. For many pharmaceutical applications, enzymes must not only deliver the required catalytic performance, but also meet stringent quality and regulatory requirements. This is particularly relevant for oligonucleotide therapeutics, which are administered parenterally and therefore require tight control of impurities such as endotoxins, host cell proteins (HCPs) and residual nucleic acids.

One example is the purification of RNA ligase (RNAL) enzymes used in enzymatic oligonucleotide assembly. While recombinant expression in *E. coli* remains the most practical manufacturing route for many enzymes, downstream purification is essential to reduce endotoxin levels and remove process-related impurities. Building on experience gained through enzyme development and protein processing programmes, Almac has developed scalable purification processes capable of supporting the production of increasingly large quantities of highly purified enzymes for both internal manufacturing programmes and external clients.

Another important area is enzyme immobilisation, a technology that offers significant advantages for industrial manufacturing. Immobilised enzymes can often be recovered and reused across multiple batches, enabling higher productivity while simplifying catalyst separation through straightforward filtration steps. They can also facilitate process intensification by allowing higher catalyst loadings and reduced cycle times.⁵

As biocatalysis continues to evolve, the ability to manufacture, purify and formulate enzymes at scale is becoming an increasingly important component of translating innovative enzyme technologies into commercially viable products and processes.

Expanding the Biooxidation Toolbox

While reductases and lipases remain the most widely used biocatalysts in pharmaceutical manufacturing due to their robustness, predictability and proven track record at scale, increasing attention is now being given to oxidative enzymes capable of performing more complex transformations. Selective oxidation reactions have traditionally represented some of the most challenging steps in synthetic chemistry, often requiring multiple reaction steps, aggressive reagents or extensive process optimisation to achieve the desired level of chemo-, regio- or stereoselectivity.

Recent advances in enzyme discovery and engineering are helping to overcome these challenges. One notable example is the growing application of Baeyer-Villiger monooxygenases (BVMOs), which have demonstrated utility in the selective synthesis of chiral intermediates, including sulfoxides of pharmaceutical interest. As non-heme enzymes, BVMOs can offer advantages in stability, solvent tolerance and catalyst efficiency compared with some traditional oxygenase systems, making them increasingly attractive for industrial applications.

Looking ahead, the range of available biooxidation reactions is expected to expand further as new enzyme classes are identified and engineered for process-scale use. In particular, α -ketoglutarate-dependent oxygenases are attracting considerable interest due to their ability to perform highly selective oxidation reactions that are often difficult to achieve using conventional chemistry. As understanding of these enzymes continues to grow, they have the potential to significantly broaden the biocatalytic toolbox available to pharmaceutical process chemists, opening new routes to complex molecular architectures and further extending the reach of enzyme-enabled synthesis.

The Future of Biocatalysis

Biocatalysis has evolved from a specialist technology used for a limited number of transformations into a mainstream component of pharmaceutical process development. Advances in enzyme discovery, protein engineering and process intensification have expanded the range of reactions that can be performed biocatalytically and accelerated the adoption of enzymes across both clinical and commercial manufacturing.

Looking ahead, the continued growth of biologics is expected to create new opportunities for biocatalytic manufacturing. Peptides, oligonucleotides and antibody-drug conjugates (ADCs) are becoming increasingly important components of the pharmaceutical pipeline, bringing new synthetic challenges that are well suited to enzymatic solutions. At the same time, demand for small molecule medicines remains strong, ensuring that established biocatalytic transformations, particularly those involving reductases and hydrolases, will continue to play a central role in pharmaceutical manufacture for years to come.

The next phase of growth is likely to be driven by increasingly sophisticated enzyme technologies. As enzyme engineering capabilities continue to improve, biocatalysts are being developed with enhanced stability, productivity and substrate scope, enabling their use in more demanding manufacturing environments. Emerging areas such as enzymatic oligonucleotide assembly, solution-phase peptide ligation and selective



biooxidation are demonstrating how enzymes can address challenges that are often difficult to solve using conventional chemistry alone.

The transformation of biocatalysis from a niche route-optimisation tool into a cornerstone manufacturing technology has been nothing short of remarkable, and the journey is far from over. Advances in enzyme discovery, engineering and process design are continually expanding the boundaries of what is possible, enabling chemistries once considered inaccessible to become routine at industrial scale. As the pharmaceutical industry pursues ever greater efficiency, selectivity and sustainability, biocatalysis is poised to play a defining role in the next generation of drug manufacturing, bridging cutting-edge science with the practical realities of global medicine supply. The future of biocatalysis is exceptionally bright and we look forward with great excitement to the innovations and opportunities that lie ahead.

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Tom Moody

Prof. Tom Moody is Vice President of Technology Development and Commercialisation for Almac Sciences and Arran Chemical Company. He holds a BSc in Chemistry and a PhD in Physical Organic Chemistry from Queen's University Belfast, along with a master's degree in business. He has authored more than 50 publications and patents and leads multidisciplinary teams advancing chemistry and biocatalysis solutions for pharmaceutical development worldwide.



Dr. Stefan Mix

Dr. Stefan Mix is Associate Director, Biocatalysis for Almac Sciences. He holds a Diploma in Chemistry and a doctorate from the Technical University of Berlin, where he specialised in stereoselective synthetic methodology and olefin metathesis. Since joining Almac in 2005, he has developed expertise in biocatalysis, protein engineering and process development, helping to build Almac's manufacturing network and technical capabilities.