Organic Process Research & Development **2011,** *15,* 173–174

Editorial

Biocatalysis: The Road Ahead

Big pharma is undergoing a major, timely transformation in its history. This is fueled by several external pressures including the patent cliff, rising generic competition, the drying pipeline, USA healthcare reform, the lingering global recession, and a greater scrutiny by the regulatory agencies worldwide. Furthermore, trends in approval of new molecular entities have been falling steadily (44 in 1996 vs 27 in 2008) despite doubling of research funding since 1991. To mitigate these trends, big pharma has been attempting to reinvent itself by streamlining operations, outsourcing many of its noncore activities, setting up "autonomous" business units to focus on fewer therapeutic areas, and implementing science-based diversification (biosimilars, biomarkers, imaging, molecular profiling, bioinformatics) to increase the probability of success of preclinical candidates entering clinical trial.

The pharma industry is $780 B worldwide, compound annual growth rate (CAGR) 7%; the global biotech market is $70 B (CAGR 16.8%). Although the biotech industry has grown moderately in the past few years, it still outpaces pharma because it is least prone to the onslaught of generics (CAGR 14%). The projected growth rates of biologics is 13% (CAGR), with mAb leading the growth with 21% CAGR, compared with a flat rate for small-molecule drugs. Consequently there has been a major shift of direction by pharma (GSK, AZ, Merck, Pfizer) in recent years toward building biologics capabilities to complement its small-molecule pipeline. This is followed by significant activities in L&A (Licensing and Acquisitions), technology partnerships, and M&A (Mergers and Acquisitions) with an intense competition amongst pharma to snap up biotech assets in multimillion dollar deals (hot areas being oncology, infectious diseases, CNS, immunology, orphan drugs). Notable examples are the acquisition of MedImmune by AZ ($15.6 B), Pfizer/Wyeth ($60 B), and Merck/SP ($41 B). With a renewed focus on a balanced portfolio of small molecules, biologics, and vaccines as well as a major effort toward external partnerships and outsourcing, pharma is well poised to transform its fortunes to realize a greater shareholder value.

Biocatalysis (the use of enzymes/microorganisms, plant/algae) in pharmaceutical (Red biotech) and industrial biotech (White biotech) applications has been truly transformative on many different levels. The industry has been quick to adopt "green technologies" to reduce environmental impact, reduce manufacturing costs/footprint, replace multistep complex synthetic routes with a single enzymatic step, eliminating toxic solvents/reagents, and/or bypassing competitor's patents. Applications include pharmaceuticals (chiral intermediates), biofuels (bioethanol, biobutanol), cosmoceuticals (flavours and fragrances, anti-wrinkle enzymes), food/nutrition (glucose isomerase, digestive/processing enzymes), diagnostics (DNA/antibody-based detection systems), personal care (proteases for detergent industry), nutraceuticals (vitamin C using pathway engineering), biopolymers for fibers/packaging (Sorona, polylactic acids), fine chemicals (6-aminopencillinic acid via Pen-G acylase), and agrochemicals (*S*-methoxyisopropylamine herbicide) to name a few.

The recent US Government Stimulus Act has provided huge incentives for biotech to develop "clean technologies" to replace fossil fuels. Many start-ups have refocused R&D efforts for commercial production of key chemicals from agricultural vs petrochemical feedstocks (succinic acid, Roquette/DSM) and/or production of biofuels (Virgin Atlantic). With rising oil prices and growing signs of economic recovery, particularly in Asian markets, the drivers for cleantech remain strong. In 2010, Amyris Biotechnologies (CA, USA) raised $85 M in an IPO (initial public offering) to produce ethanol from Brazilian sugar cane, whereas Codexis (CA, USA) raised $78 M for its IPO for corporate diversification to include biofuels (Royal Dutch Shell/Chevron) as well as expanding its biocatalysts offering to pharma (Merck/Pfizer).

Another area of considerable growth is the enzyme replacement therapy (ERT) orphan drug market ($40 B). Midsize pharma (Genzyme, Shire) have cornered this market to treat a variety of orphan indications including Fabry disease (α-glycosidase deficiency) and Gaucher disease (α-glucocerebrosidase deficiency, marketed as Cerezyme by Genzyme). Mammalian (CHO cells), human and/or plant (carrot) cell lines have been used to produce the correct glycoforms of these enzymes for human use. It is worth noting that a typical treatment course for Cerezyme is $200,000 for children and $600,000 for adults. This compares with $35,000 for Rituxan (mAb therapy for rheumatoid arthritis, Genentech). Given such huge upsides, it is not surprising to see the recent move by pharma to diversify into the orphan ERT space (Protalix/Pfizer).

In the 1980s−1990s several big pharma (GSK, Merck, BMS, Pfizer) had established biocatalysis groups to complement their small-molecule programmes. At GSK, we had developed multitonne-scale enzymic processes that were crucial to the market launch of several key multibillion dollar products; Epivir and Abacavir (anti-HIV), and Relenza (anti-flu). Such success stories had helped put biocatalysis firmly on the pharmaceutical map. As enzymic and fermentation-based processes became fully integrated into the main-stream pharma R&D, in early 2000 we saw a growing trend towards outsourcing to drive costs down. Contract Manufacturing Organizations (CMO), with established biocatalysis capabilities, entered partnerships with big pharma by offering fee-for-services or strategic alliances. Nowadays, pharma is increasingly focusing on its core strength in discovery/marketing and less on manufacturing. Ironically, we have recently seen a resurgence of biocatalysis in the generics sector as evident by a flurry of activities by Indian

10.1021/op100316t
Published on Web 12/07/2010

generics snapping up European assets (Nicholas Primal/Avecia; Dr Reddy's/Dow Biocatalysis). Interestingly, the generics also seem to have followed a strategy similar to that of pharma on biosimilars to complement the next phase of its growth (Teva/Lonza).

I had the privilege to be the guest editor for the first special biocatalysis issue in 2002 (25 papers). This was followed by a successful second edition in 2006 (19 Papers). The current issue (20 papers) covers both the Red and White biotech. The scope includes (1) the use of biocatalysts (isolated/immobilised enzymes, whole cells) for production of small molecules, chiral intermediates, natural products and (2) chemoenzymatic or fermentation-based processes for industrial biotech applications (biofuels, specialty chemicals). We are fortunate to have our colleagues from BIO (Bio Industry Organisation) and many distinguished international experts contribute to this special issue. I am indebted to the Editor-in-Chief (Trevor Laird) and Scientific Update (Sue Parsons) for their dedication to make this a truly "special" issue.

We have indeed come the full circle with biocatalysis in our industry, and it is gratifying to see its wide applicability in many different fields. We envisage that biocatalysis will continue to play an important role in route development and IP generation in big pharma R&D in the near future for the next generation of chiral drugs.

Mahmoud Mahmoudian
Member of the Editorial Advisory Board;
E-mail: mm6382@yahoo.co.uk

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