Biotechnology and life sciences industries – the challenges ahead

What are the scientific developments driving the biotech and life sciences sector, and how are evolving public policy and legal frameworks changing the scene? And what of the challenges ahead? Internationally recognised authority Dr Lincoln Tsang addresses these critical questions ...

FOLLOWING AN ECONOMIC slowdown in 2001 and 2002, the global biotechnology and life sciences industries have since shown signs of recovery. Some commentators suggest that this recovery is a measured process. Investors and companies are taking a more realistic and cautious view of research and development of novel products and technology platforms. Companies are less inclined to acquire experimental products without some clinical human exposure data.

The relationship between established pharmaceutical companies and small-to-medium-size biotechnology companies is changing too. It is said that the traditional approach to outlicensing deals – with biotechnology companies receiving milestones and royalties with no further direct involvement in the project – is falling out of fashion. The small biotechnology companies are becoming more sophisticated, and the big pharmaceutical companies recognise that they need to look to external innovation routinely to drive company growth in the R&D pipeline.

Collaboration - but on what terms?

In the case of *Cambridge Antibody Technology v Abbott Biotechnology Ltd*, the High Court in England and Wales considered a dispute founded on two licence agreements entered into in 1993 and 1995 in which CAT licensed its patented phage display library technology to Knoll (subsequently acquired by Abbott). Abbott then used the technology to manufacture a monoclonal antibody called Humira, which has been authorised for treating rheumatoid arthritis. The central point of the dispute was the royalty-stacking provisions of the agreements, which provided that Abbott would pay CAT a royalty of just over 5% of net sales but was permitted to offset half of royalties (which were capped at 2%) paid to third parties in respect of other patented technology that Abbott licensed to develop Humira. Abbott argued that it was entitled to require CAT to share half of the royalty burden it had for all technology used during the product development and production. CAT, however, argued that it should have been paid, and should continue to be paid, the full 5% without deductions. The Court ruled in favour of CAT's construction of the royalty-sharing provisions of the licence, and considered that this interpretation was consistent with all the other provisions of the licence and that it made commercial sense. In March 2005, Abbott was granted leave to appeal because there was compelling reason for the case to be heard, and there is a real prospect of the appeal being successful.

Scientific developments

There have been breathtaking developments in life sciences and biotechnology in recent years with the discovery of new targets for improving the prevention, diagnosis and treatment of a great number of diseases. Scientists have been developing novel ways to handle, manipulate and deliver biological materials, including genes, tissues and

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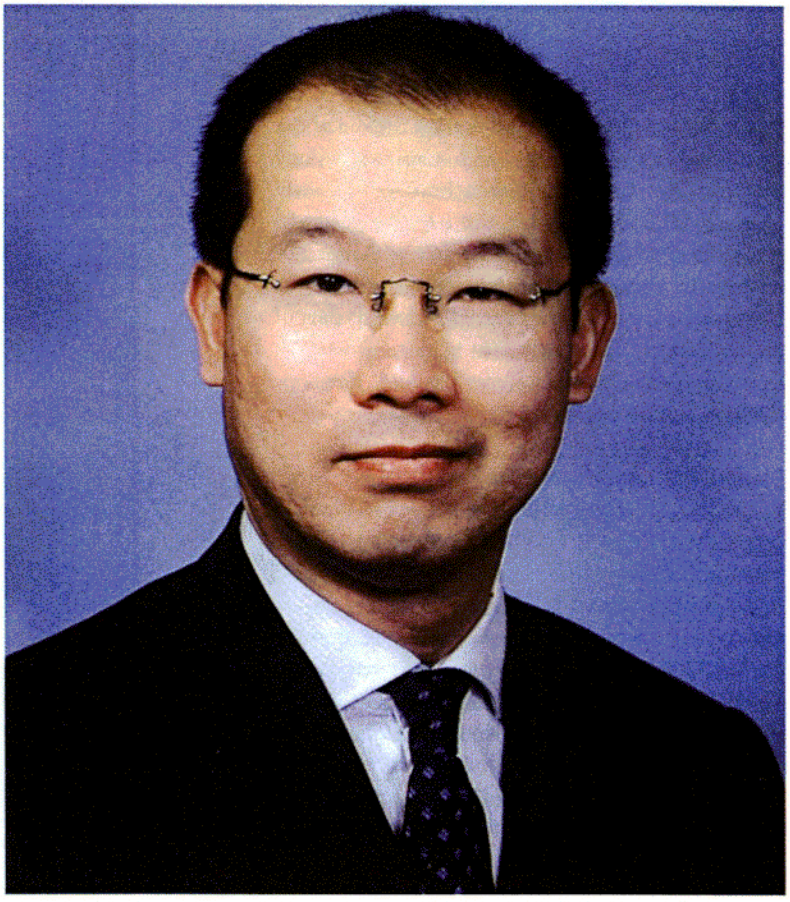

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cells, into the body to combat a wide array of symptoms and diseases. Over the past 30 years, more receptor- or target-specific biological products have been developed and approved for combating many life-threatening or debilitating diseases, some of them considered as rare – commonly known as orphan diseases.

Traditional biotechnology to emerging technologies

Since the 1980s, medicines arising from the application of recombinant DNA (cutting and rejoining of pieces of DNA) and hybridoma (fusion of cells to allow them to grow in cultures) technologies are already in clinical use, and the search for innovative developments in new areas of biotechnology is still ongoing. For example, the combination of these two technologies has allowed manufacturers to produce a wide array of target-specific monoclonal antibodies for treating chronic diseases, such as Crohn's disease and rheumatoid arthritis, and debilitating disease, such as myocardial infarction, whilst at the same time minimising the unwanted immunological response to murine monoclonal antibodies, commonly known as human antimouse antibodies (HAMAs), by removing the HAMA-inducing murine constant region gene sequences and replacing them with human constant region sequences.

Progress in the understanding of biochemistry, cell and molecular biology, genetics, material science and biomedical engineering has stimulated ▸

interest in the clinical development of cell- or tissue-based therapeutic products for treating individuals suffering from life-threatening or seriously debilitating conditions that may not be amenable to conventional clinical interventions.

Combination products

Increasingly, one sees greater convergence of drug and medical device manufacturers in developing novel approaches, such as combination products. New challenges remain as to how such products should be classified and regulated.

Unlike the United States Food and Drug Administration (US FDA), which has established an office to designate and regulate combination products, the situation in the European Union is confusing, resulting in unnecessary delays. Moreover, in some instances, products have been reported to be wrongly classified as medicinal products. The confusing regulatory scene in the EU should be urgently addressed; otherwise, the EU will be at risk of losing its competitive edge in developing such products.

Nanobiotechnology

Most recently, we have been witnessing the emergence of another field in which the physical, chemical and biological sciences are converging – commonly called nanotechnology. The technology involves anything with structures less than 100 nanometres in size, according to the US Government's National Nanotechnology Initiative. The commercial potential of this technology is immense because one can utilise the nanostructured materials for drug delivery and tissue engineering for regenerating injured or damaged tissues. This kind of miniaturisation technology will pave the way for developing novel diagnostic tests important for stratifying patient populations according to their genotype or phenotype. It is projected that the overall market impact of the combined biotechnology and nanotechnology platforms (so called nanobiotechnology) is likely to reach US$300bn within the next 12 years. In recognition of the potential benefit of nanotechnology, the European Commission proposes in its *Communication 2004* a number of actions as part of an integrated approach to maintaining and strengthening European research and development in nanosciences and nanotechnologies.

Diagnostics and biomarkers

While the life sciences market is heavily focused on products rather than platforms, the latter have become increasingly important in developing novel approaches to identifying new targets for developing new medicines and diagnostic devices. The technology continually shapes the way diseases are diagnosed, monitored and treated. The postgenomic revolution paves the way for greater convergence in product development between the medicines and devices sectors.

In the postgenomic era, the scientific community is embarking on the major task of decoding genomic information, sometimes called functional genomics, to translate the sequence information into biological functions, using high-throughput technology such as bioinformatics. This process is pivotal to identifying new therapeutic targets for product development including medicines as well as devices, such as in-vitro diagnostics using microarray technology, which permits the simultaneous processing of thousands of specimens to detect expression of multiple genes that may contribute to the aetiology of a disease. For example, the identification of cancer cell markers allows us to develop diagnostic tests for screening; molecular tests based on DNA methylation have been considered to improve cancer therapy. It has been suggested that the advent of genetic and genomic

testing for the stratification of patients and diseases will revolutionise the management of medicine and prescribing. It is because such an approach will allow for differential dosing based on genotype and screen out individuals that are most susceptible to adverse events.

Development of biomarkers

Use of clinical biomarkers in the discovery and development of drugs has also been under discussion by the regulatory agencies and companies with an interest in drug–device combinations. Biological markers, or biomarkers, are distinguishable from clinical endpoints in that a biomarker is an objective measure and evaluation of a characteristic as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. A biomarker established to substitute for a clinical endpoint is generally known as a surrogate endpoint. One may use epidemiological, therapeutic, pathophysiological or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm.

It remains, however, to be seen as to whether regulatory bodies are generally receptive to proposals for use of biomarkers as endpoints for presuming clinical activity of a product. It is being discussed that the use of biomarkers coupled with the concept of "conditional approval", which demands that companies undertake further clinical studies to fully elucidate the risk/benefit balance, may be the way forward.

Emerging technology based on gene transfer and tissues and cells

The initial aim of gene transfer was to use this approach to correct single-gene defects. However, at present, over 60% of the clinical trials undertaken on a worldwide basis relate to potential use of gene transfer for treating cancers. Some of these products have reached mid- or late-stage clinical development. The first gene therapy product was approved at the beginning of 2004 by the Chinese State Food and Drug Administration using a type of virus as a vehicle for treating head and neck cancer.

Most recently, nonvirally based delivery approaches using transposon- or integrase-mediated processes to facilitate gene insertion have been exploited. That said, the safety of gene transfer has been under constant review by the scientific community as well as the regulatory agencies, given the unpredictable nature of the gene transfer system.

Most recently, the relationship between the use of a retroviral delivery vehicle and the induction of leukaemia has refocused the importance of patient monitoring for risk management and for reappraisal of risk/benefit on a continuous basis.

Tissue- and cell-based products

It should be noted that there has been a long history of using mammalian cells as substrates for the production of therapeutic and prophylactic medicinal products such as human diploid fibroblast cells and other mammalian cells. The principles for the quality and safety evaluation of cell substrates are well established and have been published in various international and region-specific regulatory guidelines.

While products based on small molecules will continue to be developed as the mainstream products for therapeutic modalities because of their ease of manufacture and scale-up, certain chronic conditions or serious genetically predisposed conditions are inadequately addressed by ▸

existing drugs or surgical interventions. Cell- and tissue-based products seem to be an attractive approach to regenerating tissues that are damaged or to using them as the delivery vehicle for mounting immune response to treat diseases such as cancer.

Research progress in advancing the understanding of the genomic plasticity of stem cells has rendered them one of the most fascinating areas of biology today. There is now a body of evidence to demonstrate that pluripotential stem cells from a variety of sources can be induced to differentiate into any of several cell lineages. These scientific endeavours have opened up an enormous potential opportunity for all types of cell-based therapeutics. The plasticity of stem cells could therefore be exploited to create, under defined cultivation conditions, any cell or tissue type that is required for any particular clinical application, and may obviate the need to harvest specific cell types. Approaches include the use of adult, fetal and embryonic stem cells. An example of the first is the differentiation of bone marrow-derived stem cells into endothelial cells.

Interest in the development of embryonic stem cell research and its relationship with cloning has also sparked off great controversies, some of which have precipitated in challenges before courts. For example, in the UK, the Pro-Life Alliance has tested the validity of the UK government's long-held position that the primary legislation was sufficient in scope to encompass any proposed development of human cloning, including use of the process of cell nuclear replacement.

There remains uncertainty about the regulation of tissue- and cell-based products. The US FDA has made a policy decision that the Agency has jurisdiction to oversee the approval of such products under the Public Health Services Act to prevent the introduction, transmission and spread of communicable diseases. The EU has been relatively slow to respond to this regulatory challenge. Moreover, the EU regulatory framework for tissue- and cell-based products is complex and lacks clarity in many respects. The recently adopted pan-European Directive aims at setting out the common standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells. The Directive is sufficiently wide-ranging to cover all tissues and cells used for "human application" and will include the use of cells and tissues in reproductive medicine and their extracorporeal use. The regulatory principles underpinning the European law are, to an extent, similar to the traditional approach to regulation of blood products, including control of source tissues and cells.

Changes to the European regulatory landscape affecting life sciences industry

Technology transfer

There have been major changes in various aspects of the regulatory law in the course of 2004 and the beginning of 2005. On the technology transfer front, as a result of the modernisation of the European competition framework, a new block exemption regulation on technology transfers between companies has come into effect: the Regulation on Technology Transfer Agreement ("TTBER"). The TTBER covers a broad range of activities, including pure and mixed patent and know-how licensing agreements and nonassertion agreements where one party agrees not to assert its patent, for example, against the other. The new regulation is to provide for a more liberal approach to technology licensing than the previous regime by removing

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many of the artificial and confining regulatory aspects of the old block exemption.

Licensors in the new regime are guided by a relatively small list of so-called "hardcore" restrictions, which will deny an agreement the comfort of a safe harbour. In addition, there are number of nonexemptable restrictions that, although not enjoying automatic exemption, will not cause the entire agreement to fall outside the TTBER. In addition, agreements between competitors that will benefit from the exemption where the combined market share of the parties does not exceed the threshold of 20% of the relevant technology or the relevant product market. Agreements between noncompetitors are exempted where the market share of either party does not exceed 30% of the relevant technology or the relevant product market.

Review of pharmaceutical legislation

The legislative changes have been made primarily because of the European Union enlargement after 1 May 2004. In 2004, we witnessed the completion of the review of the pharmaceutical legislation with the adoption of a new Regulation governing the so-called Centralised Procedure and the European Medicines Agency (EMEA), and an amending Directive that sets out changes made to the Code for Medicines for Human Use. The revision of the European pharmaceutical law has been said to be substantial, with as many as 200 changes to the existing rules covering administrative procedures, approval process and the regulatory powers of the competent authorities. Increased transparency of the regulatory decision, change in data exclusivity, conditional approval and support of small-to-medium-size enterprises are, to name a few, initiatives included in the new European regulatory framework.

Some view that changes made to European pharmaceutical law initiatives are critical and timely for Europe to regain its global position as the centre for pharmaceutical research and development in the face of the recent report published by the European Federation of Pharmaceutical Industries and Associations (EFPIA), which shows the vulnerability of the pharmaceutical industry in Europe in comparison with its US competitor and that Europe is fast losing its competitiveness as a locus of innovation. In addition, legislative proposals for paediatric medicines and conditional authorisations are currently in progress.

At the same time, one witnesses the continued erosion of the principle of data protection or exclusivity, particularly in matters relating to incremental research, following a series of controversial judgements made by the European Court of Justice in *Novartis, SmithKline Beecham and Lilly*. In addition, the debate of the appropriate standard for approval of follow-on biological products, or biogenerics, is ongoing on both sides of the Atlantic in light of the concern over potential clinical safety that may arise from a change to the process or formulation of a biological product. The pending case of *Sandoz v the Commission* in the European Court of First Instance may be seen as a test case to address some of the underlying regulatory issues surrounding approval of follow-on biological products.

Drug safety and penalties

The EU legislation recognises that drug safety at postapproval is critical in relation to public health protection. This is exemplified by a number of high-profile drug safety regulatory reviews carried out on both sides of the Atlantic. The revised legislation imposes more extensive and stricter postapproval surveillance, coupled with sanctions for noncompliance with regulatory requirements. The EMEA will be charged with the responsibility of coordinating the verification of pharmacovigilance compliance. It is anticipated that there will be greater scrutiny in the form of inspections to be carried out. The enforcement powers in the EU currently rest with Member States, and the measures are subject to effective, proportionate and dissuasive penalties.

In the EU, greater emphasis is now being placed on risk management. This policy coincides with the policy change in the USA made by the FDA top officials in August 2003 when the FDA unveiled a five-part strategic plan for improving the performance of the regulatory agency in its overall mission to serve public health needs. According to the former FDA Commissioner, Dr Mark McClellan, this strategic action plan is the Agency's coordinated effort to respond to some of the most challenging threats to and opportunities for public health that the FDA has ever faced. The initiative includes a science-based risk management approach to ensure consumer protection.

In addition, according to Article 84(3) of the new Regulation governing the Centralised procedure, the Commission is empowered at the request of the EMEA to impose financial penalties on the holders of marketing authorisations. In its recent proposal to implement the Regulation, the Commission considers two types of financial penalties: one relating to fines (lump sums) for the infringement of obligations in connection with the marketing authorisation, and the other relating to periodic penalties for the enforcement of measures of inquiry and of decisions finding the existence of an infringement.

In relation to the lump sum fines, it is proposed that the marketing authorisation holders may be fined not exceeding 10% of the total

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turnover in the preceding year to that in which the infringement was committed. The periodic penalty payments are currently being proposed to be set at a level not exceeding 1% of the average daily turnover in the preceding business year per day.

New challenges

The scientific endeavours in developing novel approaches to treatment of diseases of unmet clinical need will continue. These will have significant impact on the environment for investment in and regulation of such products. On this note, the EMEA has recently published its *Road Map to 2010*, in which it sets out the vision to make Europe a more competitive environment for development of pharmaceuticals. This initiative is largely driven by various high-level discussions following the Lisbon Summit's aim at "economic, social and environmental renewal".

The real question is whether this and other Community policy documents will deliver what it sets out to achieve as regards timely access to medicines and transparency in regulation decision-making. Will the regulation be responsive to new challenges identified in that report as regards application of novel technology platforms and increasing demand for partnership between industry, regulators and patient groups in developing policies? Is the regulatory standard for approving products for unmet clinical needs sufficiently transparent? Will cost containment policy through devices such as technology assessment present an additional obstacle in relation to access of innovative medicines? Will the recently agreed action plan for filing parallel scientific advice in the FDA and the EMEA help in harmonising trial design and expediting clinical development? ■