

# Innovation and regulation in the biopharmaceuticals sector

Jim Attridge

*Summary: The innovative performance of the biopharmaceutical sector has weakened over recent years, most noticeably in Europe. This article summarises research on models of the innovation process and uses them to analyse the impact of various forms of regulation and incentives on this performance.*

*Keywords: biopharmaceuticals, innovation, regulation, Europe*

This paper addresses two questions. How does biopharmaceutical innovation work? How do changes in EU market regulation impact upon the processes involved?

## Innovation processes

Investment in, and the output of the biopharmaceutical sector is a function of three areas of decision-making: (1) individual product life cycle economics; (2) market and Research and Development (R&D) product portfolio risk and return assessments; and (3) sustainable business investment models.

## Individual product life cycle models

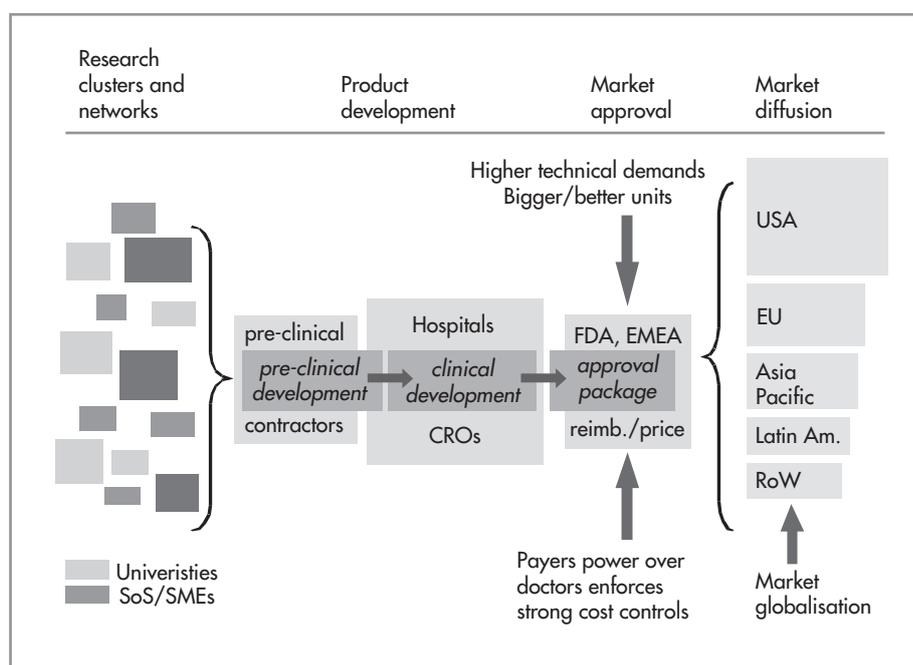
Basic models of product innovation propose a coupling process between two forces: ‘technology push’ based upon the creation of new scientific knowledge and ‘market pull’, based upon a societal need or opportunity.<sup>1</sup> Pharmaceutical innovation has been dominated by ‘technology push’, involving waves of parallel, incremental innovations in physiology, medicine, diagnostic techniques and drug therapies, underpinned by advances in biology, chemistry and other basic sciences. Up until recently the existence of a strong ‘market pull’ force, in the form of demand for better treatments has been largely taken for granted.<sup>2,3</sup>

This model has four sequential components as shown in Figure 1:<sup>3</sup>

1. Bioscience and medical knowledge creation, ranging from fundamental advances in our understanding of molecular and cellular structures and processes in living organisms, through to improved clinical knowledge of disease aetiology.
2. Discovery of molecular entities, which in principle can disrupt or block these disease processes, and can be patented as inventions.
3. Product development processes, which through laboratory and clinical work translate the molecular entity into a product, culminating in a market license to sell it.
4. The innovation diffusion process, whereby patients benefit from improved therapy and companies achieve a return on their investment.

The term ‘innovation’ is best defined as a process. Sustainable innovation is one in which incentives exist for it to be continuously repeated in a cyclical manner. Commonly, individual products are called innovations if they have passed through the complete process and have been widely adopted in clinical practice.

**Figure 1: A linear model for an individual new medicine**



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Experience shows that it takes a new medicine five to ten years and costs many hundreds of millions of euros to meet the high, legally enforced standards for efficacy, safety and quality.<sup>4</sup> This feature of the medicines innovation process distinguishes it from most other high technology sectors. Thus a classical economic model of innovation suggests that the first innovator to bring a new type of product gets a substantial 'first mover' advantage over any following competitors in the same field of innovation. However those that follow after the first entrant with incremental improvements will probably have the advantage of lower risks and lower development costs. In the biopharmaceutical sector, because of the dominant concern with safety, incremental followers in a class of medicines must perform exactly the same tests and trials required by the regulators for all medicines, incurring essentially the same costs and requiring much the same timescale.<sup>5</sup>

Over the past decade, two significant changes have occurred. At the front end of the process, more complex geographical clusters of academic centres, research institutes, 'spin-off' companies (SoS), small and medium sized enterprises (SMEs) and global pharma research centres have emerged, which create and trade knowledge. At the back end, there is increasing competition between large companies, whose core capabilities are their efficient parallel development processes and their 'global reach' – the ability to achieve timely market diffusion across developed countries.

In general innovation theory, it has proved useful to distinguish between major, or radical innovations and small, or incremental ones. At first sight, for biopharmaceuticals this can be interpreted as the first of a new class of medicines, based upon new understanding of disease processes and a new mode of action (a radical innovation) and follow-on products, which act in a similar way (incremental ones). However, closer inspection of the processes outlined in Figure 1, which lead to the sequential evolution of new product classes, suggests that the reality is more complex and variable.<sup>6</sup>

Biopharmaceuticals innovation at the product level consists of a sequence of three competitive races: (a) The 'research race' to translate original knowledge via useful potential applications into patents; (b) The 'development race' to convert the patented molecules or bio-entities into

technically approvable products; and (c) The 'commercial race' to achieve rapid international uptake of the product for the benefit of patients and to reward the innovator.

For the most part as a consequence of the patent disclosure system and largely transparent clinical research methods, competition in development is conducted in a remarkably open manner at all stages compared to other industrial sectors. In biopharmaceuticals there is little scope for gaining competitive advantage by maintaining high levels of secrecy. Insofar that a 'break-through' or radical step can be identified, it comes at the invention or patent stage and many academic and industrial individuals and centres may claim to have made a contribution to it. The patent system provides the currency through which inventors can sell their knowledge and get rewarded for their contribution.

Over the past decade, a shift in the balance of the technology base of the sector has occurred – from chemical to biological – largely led by the USA. This is a long and complex transition, which has been underway for over twenty years and is still continuing today. Its significance lies in a change in the first phase of the innovation processes in the form of a more profound understanding of disease processes in terms of molecular biology and genetic processes. This has created a dramatic increase in novel bio-markers or bio-targets; new starting points from which research can begin to find molecular entities that can interfere with disease processes in quite new ways. The molecular agents that are emerging from this new era of research may be small molecules, proteins, or biological entities such as monoclonal antibodies. As with all step changes in technology, although opening up new vistas for research, it is in itself highly disruptive of the entire process of development and the economics of innovation. It continues to offer previously unimaginable opportunities to create new therapies to address unmet medical need in some of the most intractable diseases. Some evidence suggests that the very wide scope of new options that have opened up at this early stage, with little experience as to which avenues of research might be most attractive, has of itself contributed to the lower productivity of R&D in recent years.

It has led to the emergence of specialised, biotechnology based companies, a few of which have grown entrepreneurially into

major players, albeit operating in limited disease segments. In response, leading companies have adapted both their strategies and organisational forms and currently are competing to collaborate with or acquire biotech-based SME companies that have sound patent positions.<sup>6</sup>

Efficiency in the development race benefits from highly competitive investment and the organisational capabilities of large companies. The lead in the race to market for a new class of medicines may change hands many times. Also there is little correlation between the order of market entry and the combination of benefit and risk attributes that individual products offer. Thus in the light of mature experience in deploying a new therapeutic class of products, it may be the third, fourth, or fifth entrant which offers the best treatment for a typical patient.<sup>6</sup> However, others may offer the optimal treatment for more precisely defined patient sub-sets. The order of market entry, often seen as a sign of priority or leadership in achieving success in innovation to the casual observer, is as likely to be a consequence of relative competitiveness in the development race, as a measure of inventiveness or inherent originality of the product active ingredient *per se*.

Therefore simple classifications of new medicines within a class as either 'break-through' or 'me-too',<sup>8</sup> based upon the order of market entry is inconsistent with numerous studies of the clinical value of individual products.<sup>9,10</sup> Hence, also the distinction between radical and incremental innovation can be potentially misleading when applied to this sector, where it might be best to reserve the term 'radical' for the class as a whole and to regard *all* products within it as incremental alternatives.

#### Market and R&D portfolio models

Creating and sustaining a portfolio of R&D projects, which will feed through into a market product portfolio, is a crucial issue in sustaining innovation as a routine, industrial process as opposed to a discontinuous, entrepreneurial one.<sup>11</sup> The overall R&D strategy defines the allocation of investments to disease areas. These strategic decisions are long-term because building the necessary capabilities to compete effectively in a given disease sector takes many years. It requires teams with diverse scientific skills, facilities and external relationships, which cannot easily

be replicated or transferred.

Companies continuously review the scientific, medical and commercial viability of a portfolio of around fifty to one hundred projects and must select those that go forward and those that are terminated. Some of these are high-risk, with a low probability of commercial success, while others offer more immediate prospects of a return. Some projects will be in the earliest stages of the six to ten year time-line from early research to market approval, while others will be closer to market entry. Managing the balance of this portfolio over time requires a sophisticated mix of project evaluation techniques, experience and risk-taking judgements. As a very broad generalisation, there is a direct correlation between the risk of failure in translating a project into a clinically approvable and saleable product and its innovativeness, i.e. the more original the potential product concept, the greater the risk of failure.

For leading companies at any given point in time 70–80% of total revenue comes from no more than three to five patented products and correspondingly the prospects for new products emerging from R&D into the market over the next five years will also depend upon no more than three to five key late stage development projects. Hence the rapid failure of just one major late stage development project or an important in-market product can seriously destabilise the business of the company concerned.

### Sustainable business models

Biopharmaceutical companies are private sector entities which have a responsibility to provide both value for money to their customers and a level of return to their investors commensurate with the associated risks of loss. Investors constantly switch their investments between industrial sectors based on their prospects. For higher risk, higher return, technology-based industries there is a strong emphasis on evaluating the long-term sustainability of each sectors' business models. For biopharmaceuticals, the contents of R&D pipelines, flows of innovative new products into the market, and the decline and effective 'death' of established products at patent expiry are all scrutinised in sophisticated models.<sup>11</sup>

Recent work by Porter<sup>12</sup> shows that over the period 1992–2006 major US pharmaceuticals ranked fourth amongst industry sectors in terms of profitability (return on invested capital). On average European

pharmaceutical companies are less profitable than their US counterparts.

The spread of cheap generics across world markets has greatly reduced life cycle revenues over the past decade. A combination of improved cost efficiency through mergers and acquisitions and partial restoration of revenues by global expansion has stabilised the biopharmaceutical business model in the face of this challenge. But, currently revenues are coming under renewed pressure due to a combination of lower prices for both off- and on-patent products and the sustained period of low R&D productivity.<sup>13</sup> Projections over the next five years<sup>11</sup> suggest that if this trend continues, when taken in conjunction with a series of major product patent expiries, it will require companies to radically re-think their business models, reducing costs further to sustain acceptable returns to investors.

### The value of innovative medicines and how it is shared

Innovation creates social and economic value which is shared between stakeholders. Teece<sup>14</sup> observed that over the long run, four parties share the value generated by innovations: customers, the innovator, imitators and other suppliers. In practice, defining value and estimating shares is very difficult.

However, recent studies suggest that the share of value created which accrues to medicines innovators may be lower than is commonly believed. In a 25 year retrospective analysis of the use of innovative classes of medicines in the USA for HIV/AIDS, Philipson and Jena<sup>15</sup> assessed a societal benefit of US\$ 1,330 billion compared to only US\$ 63 billion for innovative companies. This is rather less than 5% of the estimated societal gain. They conclude, "despite the high annual costs of these drugs to patients, the low share of social surplus going to innovators raises concerns about advocating cost-effectiveness criteria that would further reduce this share, and hence reduce incentives for innovation".

Similar, recent research by Garrison *et al.*<sup>16</sup> on trastuzumab for breast cancer, and Parvinen<sup>17</sup> on schizophrenia medicines, broadly support this thesis.

### Changing patterns of regulation in Europe and their impact on innovation processes

The 'three sequential races' model, outlined above has limitations, notably it

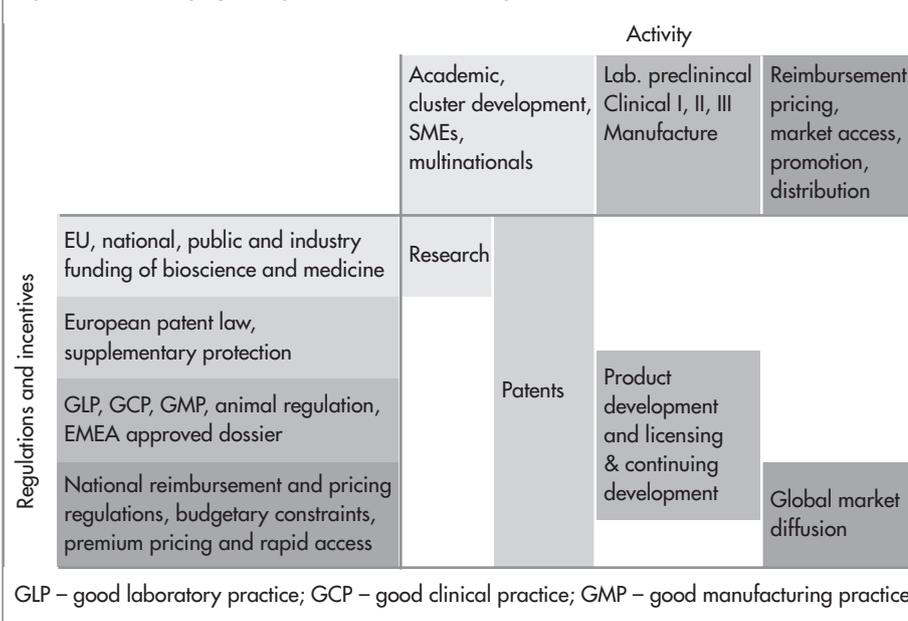
overlooks the fact that product development costs and risks continue at a high level into the market diffusion phase. However, it offers a useful framework within which to assess the impact of changing patterns of technical and market regulation in EU countries.

Recent studies<sup>18,19</sup> indicate that as part of the change to a biological basis for R&D two important new patterns are emerging in the innovation process. Firstly, the more promising bio-targets are resulting in new medicines that may prove useful over a more diverse range of diseases than in the past. This represents a greater challenge in deciding which of many options to pursue into the expensive clinical phases. Secondly this multiplicity of possible uses is pushing an even higher proportion of the clinical work to explore them in the period after the products launch for its first indication. This latter trend further exacerbates the serious problem now faced in the EU in the use of *ex-ante* health technology assessment (HTA) methods to assess the added value of new products as a basis for determining prices and reimbursed access to national markets. It appears likely that in future the full therapeutic potential of many new products will not be realised or assessable with any degree of accuracy until many years after they first enter the market.

Figure 2 juxtaposes the three phases of innovative activity with the four main areas of government regulation and incentives, which affect each of them, i.e. science and medicines public policy and funding, patent law and exclusivity regulations, EMEA (European Medicines Agency) development regulations, and member state market regulations. We now consider these combinations.

In the race to create new knowledge and invent patentable biologics or chemical entities, global investment continues apace driven by government public sector faith that bioscience will deliver both health and other social benefits and an industrial platform for competitive economic growth. The EU Commission funding through its framework research programmes for bioscience continues to grow and a new 'government-industry' collaboration, the Innovative Medicines Initiative (IMI), has been approved, which will give further impetus to 'academic-industry' collaborations across the EU. However, similar levels of investments by countries as diverse as Australia, South Korea, China and Brazil indicate the

**Figure 2: The interplay of regulation and innovative processes**



growing intensity of global competition by governments to achieve a stake in these high-tech industry sectors, but overall the prospects for the EU in this area look good.<sup>20</sup>

In the field of European patent and data exclusivity law, the cornerstone of the incentive system for investment and reward in this sector, useful progress has been made in harmonising and codifying exclusivity criteria and terms.

In the race to develop products, there has been a high profile debate as to whether the multiple requirements of agencies, such as the US FDA (Food and Drug Administration) and EMEA, were stifling innovation because they were too demanding or whether in the light of some late failures of new products in the market phase, that they were too lax and should be strengthened, regardless of the cost and time implications for innovators. An EU sponsored study in 2004<sup>13</sup> took the optimistic view that if one examined the progression of projects through the development phases, there were grounds for optimism that ‘a bulge’ of successful projects was working its way down pipelines and would restore the output of products entering the market to former levels. More recent assessments of FDA and EMEA product approvals suggest that although this has not happened yet, neither has there been any further decline in product output and it can be argued that the quality, or added value of products now coming to the market is higher than in the recent past. However, sceptics

suggest that the potential of biologics has been much overestimated.<sup>21,22</sup>

Currently, a joint FDA-EMEA review process is underway aimed at further unifying and streamlining the development requirements. Obviously the incentive to invest in R&D will improve if this can result in lower costs and shorter development time. It may also improve EU competitiveness and limit the haemorrhaging away of development activities to low cost Asian markets.

In the final phase of the innovation process – market diffusion – the race to achieve reimbursement at mutually acceptable prices and acceptance by doctors and patients the situation also looks less promising. Over recent years, many initiatives have been taken by Member States to contain annual expenditure growth in medicines to ‘affordable’ levels. Many of these have just cut prices on all products on a *force majeure* basis. Others have sought to improve the static efficiency of markets through engendering more competition between suppliers.<sup>23</sup> By far the most damaging to the innovative sector has been the initiative pioneered in Germany, therapeutic reference pricing which in effect cuts the prices of all innovative patented products in a class to the level of the cheapest generic in that class.<sup>5</sup>

The National Institute for Health and Clinical Excellence (NICE) operating in England and Wales, has led what is the latest popular approach based upon HTA in some EU markets. This in principle this holds out some prospect to innovators of

discrimination in favour of innovative products in allocating scarce funding. However, the close linkage of decision making to vague notions of health system affordability, which has led to the introduction of an upper limit cost per quality adjusted life year (Qaly) threshold for access to reimbursement, suggest that contrary to this aim, it may well discriminate against the most innovative leading edge advances.<sup>24</sup>

Regardless of the mechanism, the inescapable consequence of many such initiatives, across the twenty-seven Member States, has been to achieve short-term cost savings for the health systems and reduce revenues for suppliers of innovative products. This, by definition, reduces the dynamic efficiency of the markets and the incentives to invest in R&D. The rationale for such policies is rooted in a belief that the need for health services to contain costs is very great and the innovative industry is robust and can easily sustain its *modus operandi*, despite the cumulative impact of such interventions. The analysis in this paper suggests that, certainly for some EU companies, this premiss will not hold good for much longer.

**Conclusions**

To summarise, there is good growth in research funding and incentives to invest at the front end of the innovation process, but market opportunities for innovative new products are ever more severely constrained in EU countries at the other end of the process. While the downward pressures on off-patent sectors through generic competition is a perfectly valid approach, the current trend to then use market regulation to formally link these low generic prices to the prices of innovative patented products, forcing them down to close to generic levels is simply incompatible with sustaining a viable EU innovative sector over the long-term. The tension between these two conflicting forces is at the heart of the stress, if not distress, observed in phases II and III of clinical development decision-making where many projects are now terminated.

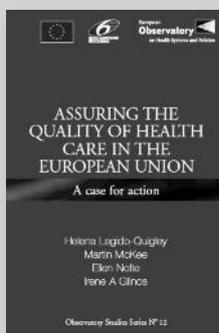
The new HTA methods offer some scope for customers and suppliers to go forward together in a rational manner, but recent English and German experience indicates that the application of ‘thresholds’, reducing to just another cost containment tool appears to be proving irresistible. In the light of this analysis of the innovation

process, the incentive for innovation is only likely to be restored, if short-term, budget driven ex-ante assessments are abandoned and the emphasis placed upon a judgemental approach to giving innovative products the 'benefit of the doubt' at launch, by allowing rapid access to reimbursement at a reasonable price, followed by a rigorous assessment three to five years later with a re-negotiation of prices and, if necessary, the terms for reimbursement.

From a global industry and consumer perspective generally, the fact that only circa 25% of industry revenues come from the EU, whereas around 45% comes from the USA may offer a degree of comfort that the latter will continue to provide the bulwark for sustaining industry business models and innovative output. However, the continuation of such a situation does not augur well for EU industrial policy aspirations to be a world class competitor in this sector in the future.

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