

Life Sciences Report 2010

The future of innovation in the biotechnology
and pharmaceutical sectors



Contents

Foreword	3
Introduction	4
The industry view	5
Industry research – key findings	9
1. The challenges facing originator pharmaceutical and biotechnology companies	14
2. Patent term extensions	17
3. Patenting strategy	22
Conclusion	26
Annex – Patent term extensions worldwide	27
Marks & Clerk contacts	29



Hugh Griffith is Co-Founder and CEO of NuCana BioMed an oncology focused biopharmaceutical company. He is actively involved in early stage biopharmaceutical companies as co-founder, director, investor and/or advisor. Hugh also serves as CEO and Gatekeeper of Alida Capital International, a specialist biopharmaceutical business angel syndicate, which he formed in 2009. As former COO of Bioenvision, Hugh led the company's operations from start-up to a global, fully integrated, NASDAQ National Market listed biopharmaceutical company. He was instrumental in increasing Bioenvision's market capitalization from \$22 million to \$345 million in 5 years, culminating in the company's successful acquisition. Hugh has extensive experience of the biopharmaceutical industry and has held numerous senior positions in Abbott Laboratories, Parke-Davis Warner Lambert and QuantaNova, and serves on the Scottish committee for the BioIndustry Association.

Foreword

The life science sector has faced extraordinary challenges over the last couple of years. Endurance through the global economic downturn has highlighted the industry's remarkable resilience, innovation and flexibility.

Accessing capital has become far more challenging and expensive, especially for early-stage companies and the funding environment will remain difficult for many biopharmaceutical companies. Venture capitalists have become more selective with a greater focus on de-risked investments, coupled with the need to retain funds for their existing portfolio companies. Also, the IPO market, although showing some signs of recovery remains largely closed. The recent wave of pharma mega-mergers and consolidation of disease targets has reduced the number of potential partners and buyers for biotech assets. However, opportunities to acquire big pharma's de-prioritised molecules are rapidly increasing, as investors look to match de-risked molecules with the right management team.

For major pharmaceutical companies, whose clinical pipelines are insufficient to replenish the lost revenues forecasted, the patent cliff continues to loom large. Numerous strategies have been adopted by pharma to counter this threat: improving R&D through restructuring to boost innovation and efficiencies both internally and with external partnerships; product diversification; expansion into new geographical markets; a shift from the blockbuster model toward targeting smaller patient populations; and, flexible approaches to pricing through discounting and health outcome guarantees. Within this environment we can expect an increase in the volume and prominence of court disputes as originator companies seek to defend and maximise the length of their patents. However, despite all these approaches the requirement for pharma to maintain earnings at their current levels will be driven by significant M&A activity.

US healthcare reform legislation is another major factor that is impacting on the life science sector. The reform aims to expand access whilst contracting costs, but will require significant efficiencies to be applied. A greater emphasis on health outcomes is anticipated and the industry will need to pay even greater attention to payer acceptance and reimbursement strategies. The 12 year period of data exclusivity from the biosimilars provision will raise the present value of existing research pipelines and significantly benefit biotechnology companies.

Companies with the ability to learn to do more with less will prosper. Efficient deployment of capital and quicker paths to critical value inflection points will provide the competitive advantage. Approaches to minimise cash burn include: lean headcount; minimal infrastructure; and, effective outsourcing to leverage expertise and economies of scale. Broadening the search for capital to include government programs, disease foundations, corporate partnerships, and risk sharing arrangements with service providers may be required. Great science is no longer enough as strong product platform differentiation from the competition in both the market and clinic is now essential.

The life science industry's resilience has always been based on innovation. Our scientific knowledge is greater than ever before, however, to successfully translate this to significant advances for patients will require us all to adapt our business models and strive for ever greater efficiencies.

A handwritten signature in black ink, appearing to read 'H. Griffith', written over a light blue horizontal line.

Hugh S Griffith
Co-Founder and CEO, NuCana BioMed

Introduction

Welcome to the Marks & Clerk Life Sciences Report 2010, assessing the state of play for the life sciences sector.

Astute followers of our annual Biotechnology Reports will note a slight departure in this year's report to those of previous years. In short, our focus this year considers the life sciences sector as a whole.

In the context of the future of pharmaceuticals – in other words, innovation – a distinction between the biotech and pharma sectors becomes rather spurious. There is little doubt that the nature of drug discovery and development has significantly changed, and the future of R&D lies in far more complex and costly products. In this environment, the pharma and biotech subsectors become inextricably interdependent and will converge yet further in the face of looming patent expiries for big pharma on its major blockbusters, and the clear threat to revenue this entails. The future of medicine is dependent on the marriage, and the fortunes, of the industry as a whole.

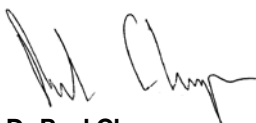
It is perhaps therefore unsurprising that at Marks & Clerk we are also seeing a greater call for advice from the life sciences sector, in particular in the area of maximising patent protection and thus the shelf-life of existing products. Our response this year is to provide more in-depth commentary in the report's later chapters, having first assessed the climate for industry in the opening section. In this, we are extremely grateful to the contribution of the 380 life sciences representatives worldwide who took part in our industry-based research – conducted by way of a detailed online survey – for making this report possible.

So, where are we now? Much has changed in the last 12 months for the life sciences industry: the biggest issues being the staging of a fragile economic recovery, and the pushing through of US healthcare reform. On this side of the Atlantic, the EU Commission continues to keep a close eye on pharmaceutical and generic drug maker practises.

There is also wide recognition that there are fewer drugs coming to market, while at the same time the industry is facing a considerable increase in generic competition. Against this background, we used this year's research to investigate the industry's perspective on innovation: namely, whether the patent system adequately rewards companies for their innovations and provides suitable recompense for the delay in bringing products to market due to necessary regulatory reviews being carried out.

In the context of innovation, it is perhaps worth emphasising that the originator drug industry and generic pharmaceutical/biologics industry must coexist. However, patent and regulatory systems need to strike a delicate balance between enabling generic entry on the one hand, whilst at the same time encouraging and rewarding true innovation on the other. Reforms which favour one branch at the expense of the other could result in far-reaching and detrimental economic and social consequences.

Once again, we would like to thank all those who took part in our research, as well as our colleagues in the Far East and Canada for providing their assistance with issues of particular relevance to their market. We hope you find the research and commentary which follows both informative and practical.



Dr Paul Chapman
Partner, Marks & Clerk LLP

63%

of respondents indicate that the climate for doing business and access to funding have improved over the last 12 months

The industry view

In order to better inform the insights and conclusions contained within this report, Marks & Clerk undertook industry research to probe the sentiment and challenges facing those working within the life sciences sector.

The outlook for the market

One of the headline themes to emerge from our research is that of an improving economic climate. A clear majority (63 per cent) of respondents indicate that the climate for doing business and access to funding have improved over the last 12 months.

This is significant in the context of our emerging from a global recession frequently cited as the most severe economic contraction since World War II. Casting our minds back to last year's 2009 industry report, the picture painted by the life sciences sector was rather more bleak.

Understandably, given the global economic situation at the time, our research was dominated by severe concerns as to risk aversion amongst investors, and the consequent funding drought that plagued the industry – particularly for smaller biotechnology start-ups at earlier stages of their drug development cycles. Fears abounded as to the level of bankruptcies expected, with many of the opinion that the existing funding structure would struggle to survive the downturn. At that time, 93 per cent believed the climate for biotech had deteriorated, with funding terms becoming increasingly onerous, yet nearly 6 in 10 (58 per cent) feared it would take beyond 12 months before investors returned to the sector.

This, of course, is not a trend limited to the pharmaceutical or biotechnology sectors. The financial crisis, which reached its peak in early 2009, cast a dark pall over investment flows in general. While the primary victims were inevitably smaller, riskier start-ups in need of funding, even traditionally defensive investment prospects such as large pharmaceuticals were hit (after an initial flight to safe-havens), as world stock markets tumbled. Since this point, the global economy has begun to recover in earnest, albeit that concern remains – and in particular for parts of the eurozone. Appetite for risk is slowly starting to return.

Increased optimism can be seen elsewhere in our survey. Nearly two-thirds (65 per cent) think that the improved economic situation means the industry now has the confidence to press ahead with acquisitions, coming good on last year's prediction that the recession would result in further industry consolidation as major pharmaceutical companies took advantage of depressed valuations. Meanwhile, 84 per cent believe the appetite is now there to strike strategic commercial collaborations with partners.

This is not to say, however, that the sentiment expressed in this year's research is overwhelmingly positive – and indeed it may be the case that market appetite for deal-making is driven more by need than desire. Already, we have seen bursts of such activity over the last two years, in spite of harsh economic conditions. Eli Lilly's \$6.5 billion takeover of cancer specialist biotech ImClone in 2008, and Roche's \$48.6 billion 2009 acquisition of Genentech are just two cases in point. Clearly, the industry anticipates that this trend will increase and intensify going forward. In the face of dwindling pipelines, big pharma may have little choice.

However, it is fair to say that the predominant concerns of respondents have shifted to longer term industry-specific problems that are coming to a head, rather than immediate economic fears.

The looming patent cliff – and its consequences

There can be no doubt that the pharmaceutical industry is reaching a critical phase with regard to R&D and the dwindling drug pipelines of originator

97%

of respondents think that the importance of patent term extensions will remain or intensify as blockbusters near the end of their patent life

companies. This is having a significant effect on both business and patenting strategies.

The market for conventional small molecule drugs is now very mature, and the development of new blockbuster drugs within this space appears to be slowing significantly. Meanwhile, a patent cliff looms for several major pharmaceutical companies over the coming years, with a number of blockbuster drugs, such as Pfizer's Lipitor®, Wyeth's Protonix® and GSK's Hycamtin®, set to come off-patent between 2010 and 2014.

This headwind is compounded by the difficulties traditional pharmaceutical companies have experienced so far in replenishing drug development pipelines with new generation biologics, whether through internal redirection of R&D, or acquisitions of smaller biotechnology companies. Over 8 in 10 (82 per cent) respondents believe that big pharma's inability to innovate sufficiently from within to replenish these pipelines will result in increased acquisitions. Over two-thirds (68 per cent) believe that we will see substantial acquisition activity within the next two years, with almost 1 in 5 claiming that this will be staged within the year.

The rush for SPCs

The solution to the patent cliff is, however, two-fold, including much deeper engagement by the industry with strategic patenting activities. Another major consequence highlighted by respondents is an increased dependence on patent term extensions (or supplementary protection certificates (SPCs) in Europe), to maximise the product life of existing products while simultaneously pursuing new R&D sources.

87 per cent of respondents claim the industry's current interest in patent term extensions/SPCs can be attributed largely to dwindling pipelines at innovator companies, while the vast majority (97 per cent) think that this trend will either remain or intensify as blockbusters near the end of their patent life.

In short, in the absence of a new generation of small molecule drugs to make obsolete the current generation of products, and in view of the difficulties in obtaining secondary follow-on patents, SPCs are rapidly becoming a vital means for originator companies to secure large parts of their revenue streams. In turn, the flaws and limitations of the SPC system are coming under increased scrutiny. Our industry participants showed notable criticism of the protections afforded by the current system, given its increasing importance to their business and strategic patenting decisions.

In particular, respondents were largely negative about the scope of SPCs, feeling that the extent and nature of the protection afforded should be widened. As the system currently stands, SPCs are in some respects far narrower than their US equivalent. While SPCs rely upon an underlying 'basic' patent, they only protect the approved active product within the scope of that patent. As such, in many cases, they cannot be used to protect combination drugs or secondary developments of a drug beyond its initial marketing approval. The vast majority of respondents to our survey suggest that this needs to change. 87 per cent believe SPCs should be granted for secondary formulations.

Over three-quarters (79 per cent) of respondents were also broadly in favour of altering the nature of SPCs so as to make them act as genuine patent term extensions – i.e. protecting the underlying invention rather than the active ingredient. In short, this would afford them precisely the same level and scope of protection as the underlying patent, and represent a radical shift in Europe towards the US approach to patent term extensions – essentially extending the term of the patent itself.

Additionally, it should be noted that while respondents were fairly evenly split over the precise question of whether the current SPC regime provides adequate compensation for the time lost in the marketing approval process (only 55 per cent thought SPCs provided inadequate compensation), there

is broad consensus (82 per cent) that the increasing cost of R&D means innovators should be given a longer term in which to market their products.

This emphasises the shifting strategic importance of the SPC. What was previously seen as a particular means of redressing the time lost to marketing approval is increasingly being seen as a necessary extension to core revenue, and to maintaining and rewarding innovation levels given increased research costs and doubts over the future R&D pipeline. Notably, over 9 in 10 (93 per cent) believe that strengthening incentives to reward the R&D undertaken at innovator companies would help boost investor appetite too.

As SPCs grow in importance, increased attention is likely to be drawn to the inconsistencies with which the supposedly unitary European system is enforced on individual national levels. However, our survey shows that this is not yet of primary concern, with almost 65 per cent stating that the system as it currently stands is implemented across Europe with reasonable consistency. There is doubtless some expectation that any inconsistency will be addressed organically as SPCs continue to grow in importance and case law is tested or reform enacted. Should it not be, this issue will likely be an increased cause for concern in the future.

The landscape in Europe

Moving away from the practical considerations of the approaching patent cliff, respondents expressed concerns over a number of regulatory and policy issues facing the sector, emanating from both the European Commission and the European Patent Office (EPO).

In July 2009, the European Commission published its report following a sector enquiry into alleged competitive abuses, delaying the market entry of generic competition. The Commission rejected root-and-branch reform to the intellectual property system, however, and instead launched a series of targeted probes where it felt there to be abuses.

As such, the general reaction from respondents to the Commission's activity was far more muted this year than last. The industry has been able to breathe a sigh of relief. However, some concerns still linger, on several fronts.

Nearly two-thirds (64 per cent) remain of the view that European policymakers are fundamentally hostile towards secondary patents for follow-on drug development. Over three-quarters (78 per cent) suggest that critics of secondary, follow-on drug development do not give sufficient recognition to the role incremental innovation plays in advancing medicine. Some 59 per cent also expect serious fines levied in the coming months as a result of the Commission's targeted investigations.

However, the European issue of predominant concern to respondents related to changes affecting their patenting strategies. In April 2010, the EPO made rule changes significantly affecting patent examination procedure and the availability of divisional filings, designed to vastly increase the speed in which patent applications are processed and thus reduce patent backlogs.

While a very slight majority (54 per cent) of respondents support the EPO's prioritisation of speed in the application process, a significant corresponding minority (of 45 per cent) place greater priority on a slower and more thorough patent process allowing for flexibility, suggesting that the EPO may have in part misjudged the industry's needs. Respondents are in broad agreement that the measures – which will force companies to make more concrete decisions about the future direction of their R&D and patenting strategies at an earlier date – are likely to be a particular burden on smaller companies with more limited resources (82 per cent). This is particularly worrying given that, as we approach the end of the 'small molecule era', the blockbusters of the future are likely to hail from smaller biotechnology outfits – the very organisations hit hardest by these reforms.

Yet the concern is also for the industry at large. 86 per cent of respondents think it essential that Europe's patent application process does not become

64%

of respondents believe European policymakers are fundamentally hostile towards secondary patents for follow-on drug development

89%

of respondents suggest that the certainty provided by US healthcare reform will result in lasting capital being attracted back into the US market in the long run

more labour-intensive, while 78 per cent believe that making patent protection as relevant and water-tight as possible is the most important consideration for the industry to safeguard R&D. The EPO's reforms, which will inevitably precipitate shifts in patenting strategy, could undermine that level of security.

A rejuvenated US market

In contrast, the picture from across the Atlantic is far sunnier. Discussion necessarily must focus on the passing of the historic healthcare bill – seemingly on the rocks only a few weeks prior to its passage – pushed through by the Obama administration, with its profound implications for the provision of US healthcare.

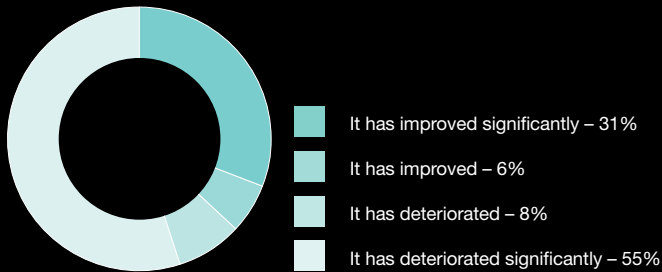
A majority of respondents reject the notion that this reform will ultimately harm drug innovation in the US, with just over 65 per cent contending that margin reduction will be offset in the long run by increased sales or that the reforms will even benefit innovation. Furthermore, 88 per cent support the longer term given to complex biologics in the bill (of 12 years data exclusivity), arguing that this creates the right level of incentive for R&D (as opposed to a five-year term for conventional small molecule products). Lastly, a compelling majority of 89 per cent suggest that the certainty provided by US healthcare reform will result in lasting capital being attracted back into the US market in the long run – presumably at the expense of other major markets, such as Europe.

Taken together, the findings suggest that we are continuing to see a more hospitable environment for drug innovation in the US than Europe. This can be inferred from a number of issues, from respondents' desire to see more patent-like scope for SPCs (as is the case with US patent term extensions), to fears that the EPO is going in the wrong direction by making patent applications more burdensome for the applicant, affecting SMEs and non-corporates in particular. 81 per cent argue that Europe's record for commercialising R&D among non-corporates is already inferior to the US, and that making patent applications more laborious could discourage inventors further and thus widen the innovation gap.

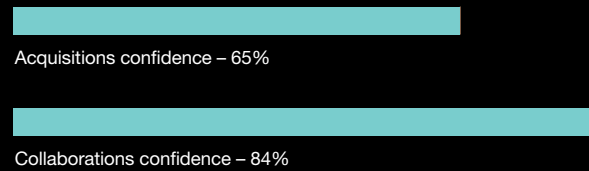
In light of this evidence, it is perhaps unsurprising that when asked directly, a clear majority of respondents (62 per cent) claimed that the US intellectual property system had better managed to reward innovation and keep up with the changing needs of the industry than Europe. A sober thought indeed.

Industry research – key findings

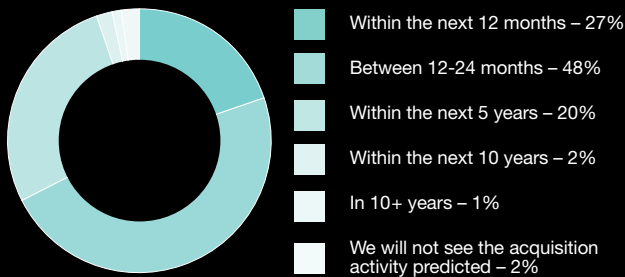
1. Extent to which the climate for business, and access to funding, has improved in the last year



2. Confidence within industry to go ahead with acquisitions and collaborations



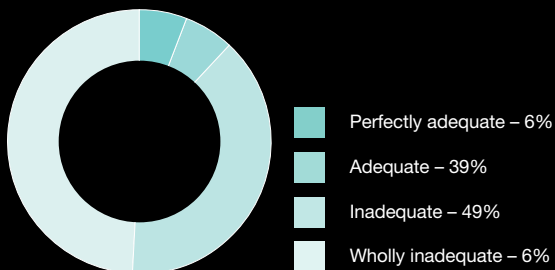
3. Timescale in which substantial acquisition activity is anticipated



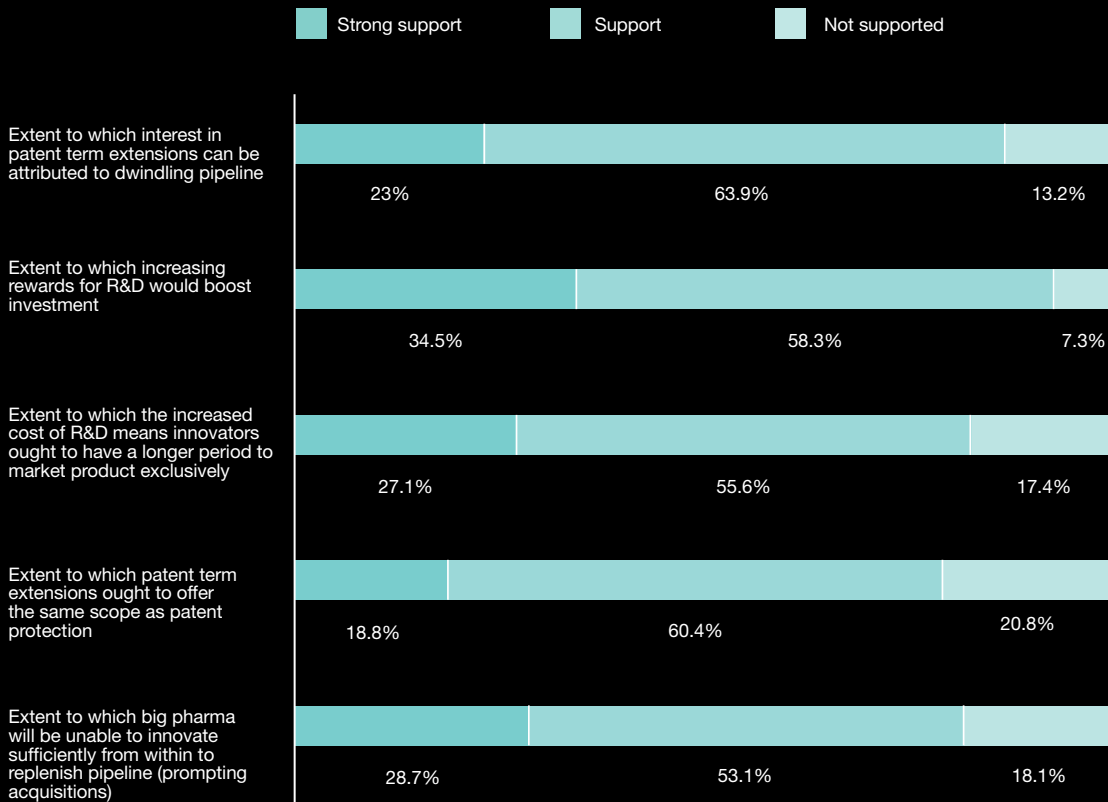
4. Improvement or decline of drug approval timescales



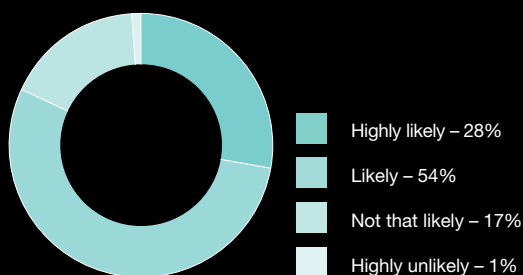
5. Adequacy of current regime for patent term extensions in compensating for time lost in drug approvals



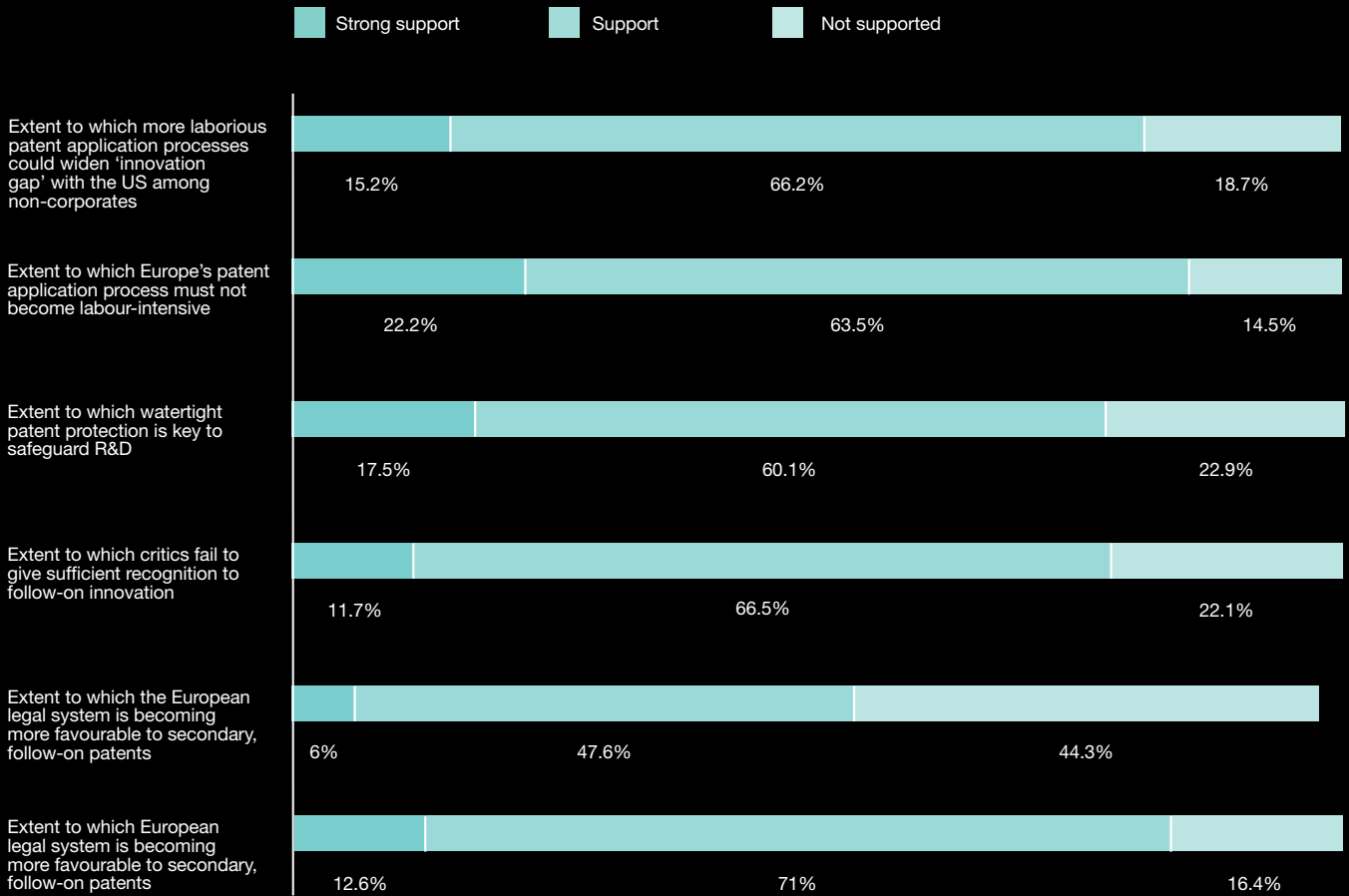
6. Views on key aspects of innovation and rewarding R&D expenditure



7. Likelihood of changes affecting the filing of patent applications at the European Patent Office being a burden on smaller companies



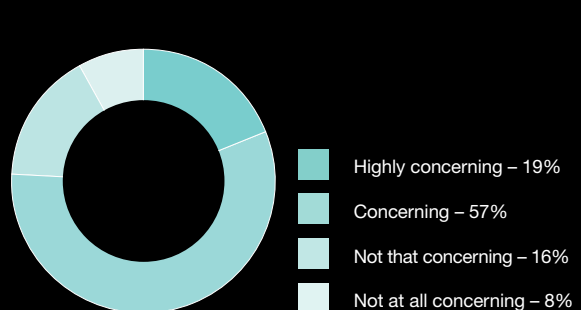
8. Views on key aspects of follow-on innovation and the European climate



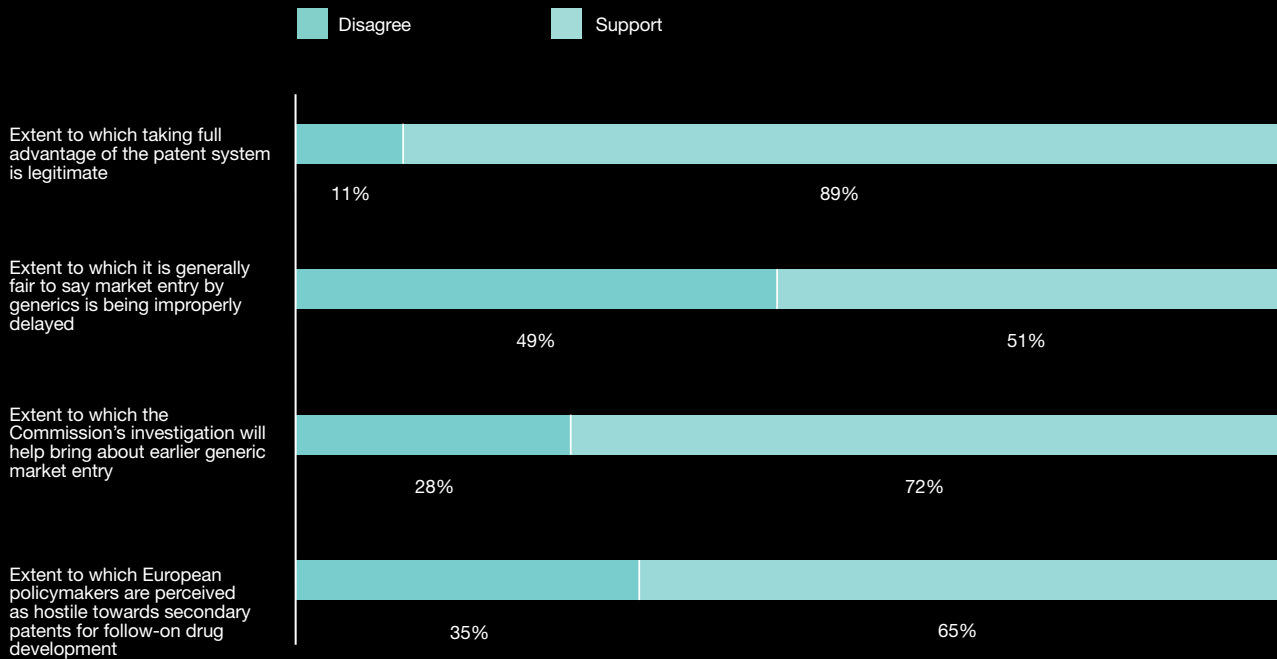
9. Circumstances in which patent settlements are justifiable



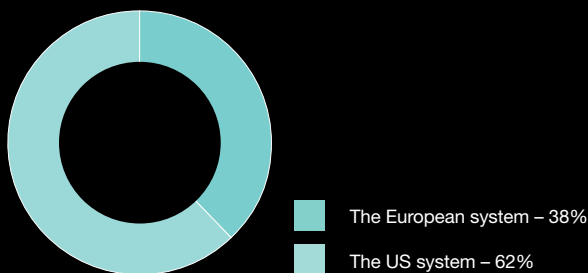
10. Extent to which the European Commission probe is concerning the industry



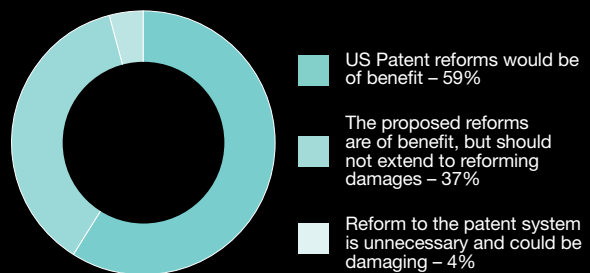
11. Views on the European Commission's probe of the pharmaceutical sector



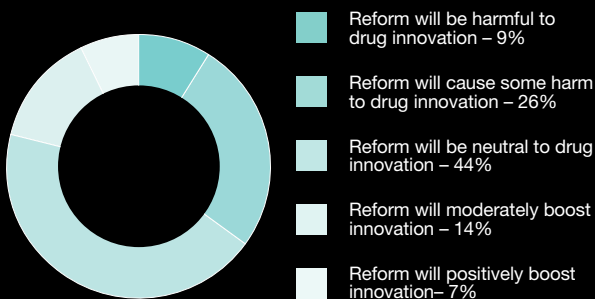
12. Extent to which the US or European IP system has managed to reward innovation and keep up with industry's needs



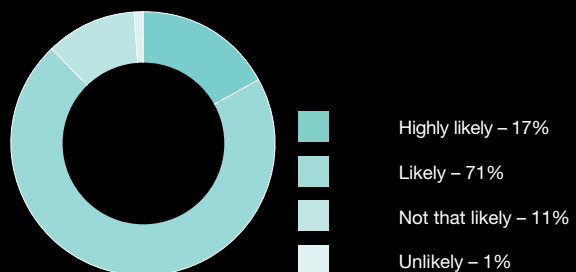
13. Support for US patent reform



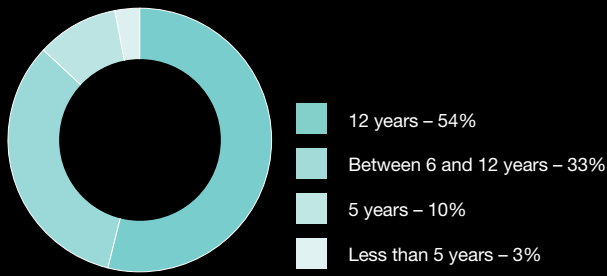
14. The extent to which US healthcare reforms will benefit or harm drug innovation



15. Likelihood of seeing lasting capital attracted back into the US market, by investors, post healthcare reform

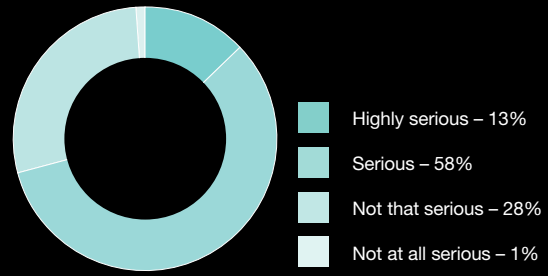


16. Length of term under which branded, complex biologics ought to enjoy data exclusivity*



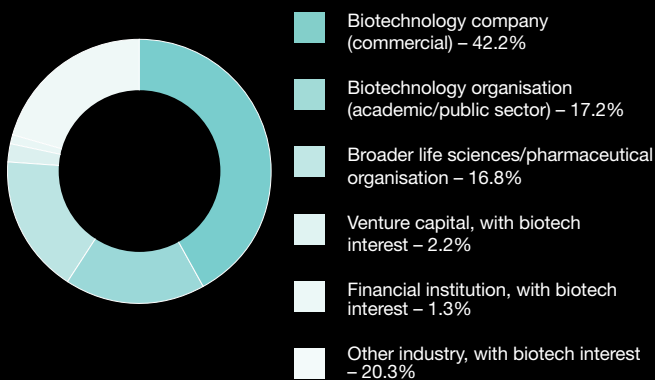
*(currently 5 years for conventional small molecule drugs, but 12 years will be allowed for biologics under the US healthcare bill)

17. Seriousness of the commercial challenge posed by biologics

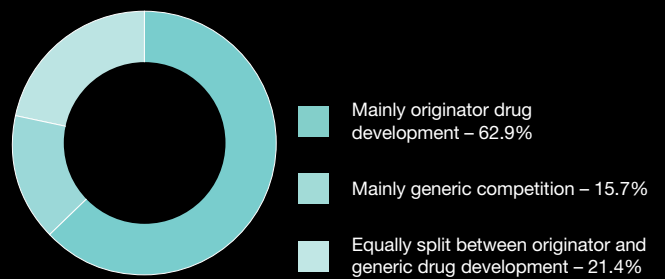


Breakdown of respondents

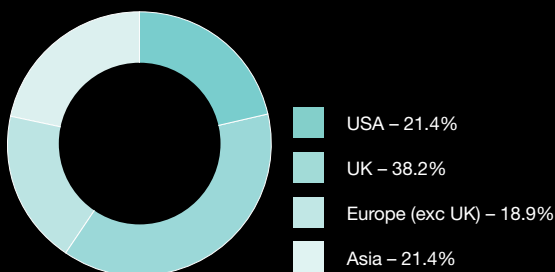
18. Type of organisation



19. Principal activity or interest



20. Geography



1. The challenges facing originator pharmaceutical and biotech companies

72%

of respondents believe the Commission's investigation will likely result in earlier typical market entry for generic competition

The European Commission's investigation into patent settlements

In Europe, on 9th December 2009, the European Commission announced that it had undertaken a series of surprise inspections of pharmaceutical companies based in the EU, following suspicions that certain entities may have been engaged in restrictive trade practices and/or were abusing their dominant positions contrary to the provisions of EU competition law.

This second wave of investigations followed hot-on-the-heels of the major enquiry into the sector that concluded in July 2009. This involved a detailed report into what many feared would amount to a series of proposals for the wholesale reform of the EU patenting system.

In fact, those particular fears were largely unfounded. While the Commission was largely critical of the number of perceived barriers to entry for generic manufacturers (and the fact that generic entry took too long in its view), it instead pressed ahead with a more targeted approach, investigating individual entities suspected of engaging in anti-competitive practices, and patent settlements in particular. It also emphasised the urgent need for an all-encompassing EU patent system (i.e. a unitary Community patent system) and, more particularly, a centralised EU patent litigation system. It established that litigation was being used as a tool to delay generic entry. Further, the Commission encouraged a review of the regulatory system to allow for more rapid approval of generic medicines via the mutual recognition and decentralised procedures.

Our research found that 76 per cent of industry participants believe the Commission's probe to be "concerning" for drugmakers, with

almost a fifth (19 per cent) claiming that it will instil worry across the industry at large. 89 per cent of respondents argued that taking full advantage of the rights afforded by the patent system should not be classed as anti-competitive and is in fact legitimate commercial practice.

The research suggests that there are some grounds for competition concerns. Just over half (51 per cent) felt it was generally fair to say that market entry was being improperly delayed, with 72 per cent believing that the Commission's intervention would likely result in earlier market entry by generics. Notably, this figure rose substantially among those companies involved in providing generic competition or engaged both in originator and generic drug manufacture. Discounting originators, two thirds (66 per cent) felt that market entry was generally subject to improper delays, and 81 per cent felt the Commission's involvement would reduce the time-lag to market entry.

So, to what has the Commission now turned its attention? Currently, details are somewhat scant but there is no doubt that the main focus appears to be carrying out investigations into those entities (both originator and generic) engaged in behaviour whereby litigations are settled on terms that unlawfully delay generic entry. In the words of the Commission itself:

"To reduce the risk that settlements between originator and generic companies are concluded at the expense of consumers, the Commission undertakes to carry out further focused monitoring of settlements that limit or delay the market entry of generic drugs. In the case of clear indications that a submission by a stakeholder intervening before a marketing authorisation body was primarily made to delay the market entry of a competitor, injured parties and

67%

of respondents think that patent settlements should be allowed

stakeholders are invited to bring relevant evidence of practices to the attention of the relevant competition authorities."

Such types of settlement may involve the payment of significant upfront or continuing payments to the generic in circumstances where, all things being equal, the generic could have legitimately entered the market earlier than it agreed to. There are other suggestions that more sophisticated systems are being put in place to keep generics at bay. Such agreements are the "restrictive trade practice" arrangements that the Commission referred to in its December 2009 press release. The Commission is also looking at those originator companies that have set up so-called patent clusters and then refuse to license generic manufacturers even those patents that are not being "worked". These are the "abuse of dominant position" activities.

The precise number of specific cases instigated by the Commission is unknown but the industry is clearly on notice that the Commission intends to leave no stone unturned in its quest to root out anti-competitive practices in the pharma sector. Patent settlement agreements must pass the stringent standards required to satisfy EU competition law principles – although the industry, on balance, argues that patent settlements are meritable. Two-thirds (67 per cent) of our respondents thought that commercial deals of this nature should be allowed, particularly in the face of potential patent attacks being mounted by generic rivals.

EU regulatory issues and biosimilars

Looking ahead, what is less certain is where the Commission stands on a formal review of EU regulatory provisions. The EU regulatory system was only relatively recently reviewed in 2004 with substantial

amendments being made to ease the way for generics to secure regulatory approval. Measures were established including the so-called Bolar-like exemption enabling generics to undertake clinical studies to prove bioequivalence without fear of transgressing third party patent rights. Furthermore, the previous patchwork national European systems of 6 or 10 years of data exclusivity were harmonised into a single EU-wide 8+2 year system for data and then marketing exclusivity, theoretically allowing generics that relied on the abridged authorisation route to enter the market exactly 10 years after originator approval was obtained.

We wait to see what further proposals are made. Possible suggestions include easing the restrictions on the use of the mutual recognition and decentralised procedures. The Commission has also indicated an interest in a more transparent pricing structure across the EU. However, given the variety of different approaches across Europe (leading in turn to a significant market for parallel trade), we would not expect early proposals for dealing with this.

What is clear, however, is that the likelihood of root and branch future reform of the patent system in Europe is significantly diminished. Not only did the final report from the Commission back away from reforming the intellectual property framework but some of its recommendations – in particular the development of a single European-wide patent – look increasingly unlikely. Where 80 per cent of last year's respondents believed a European patent would be beneficial for the industry, 84 per cent now state that its establishment looks unlikely in the near future.

This scepticism is interesting in the face of discussion about the US and European intellectual property

systems at large. Some 62 per cent of those surveyed argue that the US system has better managed to reward innovation and keep up with the industry's needs, compared with Europe. What is more, an overwhelming 96 per cent are in favour of the current US patent reforms proposed, designed to improve patent quality and set a 'reasonable royalty' requirement to contain the extent of damages paid in intellectual property related disputes.

Discussion of the US would, of course, be incomplete without consideration of Obama's much-vaunted healthcare reforms and how these will transform not only the provision of healthcare in the US but the mechanics of the industry and its future development.

These reforms go hand in hand with the fiercely debated proposals for a pathway for biosimilars. Prior to the reforms, unlike small molecule pharmaceutical products, biologic medicines had an open-ended period of data exclusivity. Legislators have now moved towards a 12 year period of data exclusivity followed by a further 6 month period in the event of a potential paediatric extension – similar in concept to the paediatric extension to Supplementary Protection Certificates (SPCs) currently available in the EU (see section 2 of this report).

Such a debate is significant in the context of the time and cost it takes to commercialise the more complex R&D of future drug development for biologics. While, encouragingly, 58 per cent of industry respondents taking part in our research felt that marketing authorisation timescales were improving, an overwhelming 83 per cent argued the increased cost of R&D meant innovators ought to be given a longer term in which to market their products with the benefits of data/marketing exclusivity. With reference to the US and the situation

regarding complex biologics – the industry had initially found itself contemplating a possible mere five-year term, replicating that afforded to conventional small molecule drugs – 88 per cent supported a longer term of exclusivity, to create sufficient incentive and boost R&D.

However, their optimism is in part tempered by the now very real commercial challenge the industry faces with biosimilars. Almost three-quarters (72 per cent) of respondents describe the commercial challenge posed by biosimilars as serious – underlining the continued competitiveness we will see around new drug innovation in the future.

The benefit of competition, from a cost perspective, is clear. There is undoubtedly the same if not more acute pressure in the US to control healthcare costs as compared to the EU. Indeed, reforms have also been proposed in the US to ban agreements that seek to delay generic entry, although notably these were absent in the final bill. While it is doubtful that the EU Commission would ever go so far, and sentiment has indeed turned in the US too, it is fair to suggest that authorities both sides of the Atlantic will be keeping a close eye on the behaviour of pharma and biotech companies in the future.

72%

of respondents describe the commercial challenge posed by biosimilars as serious

97%

of respondents think that patent term extensions will continue to be of extreme importance to the industry

2. Patent term extensions

What is an SPC?

The process of drug development is such that arriving at an effective clinical formulation, and obtaining authorisation to place a drug on the market, can take several years. This delay eats into the effective patent term. Supplementary Protection Certificates (SPCs) are intended to compensate for the time spent in trials, development and subsequently obtaining regulatory approval for medicinal products¹, by providing additional protection for the active ingredient(s) of a medicinal product after the normal 20 year patent term has expired. The term of the SPC depends on the delay between patent filing and marketing approval – it is calculated as the delay minus five years, to a maximum of five years.

Although all patent term extension systems share basic similarities in that they are intended to compensate for patent protection lost as a result of delays leading to marketing authorisation, they differ significantly in detail. Some countries offer no extension at all, while others restrict extension to one patent per product – but that concept of itself needs careful review and understanding.

A brief comparison of some national systems for patent term extension is given in the Annex.

The use of patent term extensions (PTEs) to compensate for delays in carrying out the pre-clinical and clinical trials necessary to obtain regulatory approval is a key element of ensuring that an approved medicinal product has as long a period of exclusivity as possible.

Article 3 of the Supplementary Protection Certificate (SPC) Regulation sets out the requirements for obtaining an SPC – the European form of patent term extension. Briefly, the authorised “medicinal product” contains the “product” (the active ingredient(s)). Excipients, diluents, and other components may be included in the medicinal product, but are not part of the product. The product must be protected by a “basic patent” in force at the time of filing the SPC, and is any patent designated by the patentee for obtaining an SPC. (The terms in quotes are given specific definitions by the SPC regulation.) There is no requirement that the same basic patent is chosen in different territories; there may be cases when it can be advantageous to select different patents for reasons of local validity or duration.

The economic importance of term extensions is considerable: for example, the basic patent in Europe on Prozac[®] (fluoxetine) expired in 1995. In the UK, where a five-year term SPC had been obtained, almost 80 per cent of sales revenue over a ten-year period was generated in that five-year term. In Germany, where there was no SPC protection, sales declined with the early entry into the market of several generic competitors².

Furthermore, the strategic importance of patent term extensions is growing for an industry faced with the problem of a dwindling pipeline for new products. To put this in context, by 2014, \$63 billion in yearly revenue will be eroded by patent expiries, according to Datamonitor.

In this environment, eking out the maximum shelf-life of protection available for existing products takes on newfound significance. An overwhelming 97 per cent of industry participants thought that patent term extensions would continue to be of extreme importance to the industry, with over half (53 per cent) predicting that this situation would intensify due to big pharma’s reliance on them as blockbusters near the end of their patent life.

Yet at the same time as highlighting the industry’s reliance on PTEs, life sciences companies also express some dissatisfaction with and criticism of the system designed to protect and reward their innovation. Some 56% feel that the current regime inadequately compensates patent holders for the time lost in obtaining regulatory approval

In relation to the cost of that R&D, their dissatisfaction is much more keenly felt still. 83 per cent argue that the increasing cost of R&D means innovators ought to be given a longer term in which they can market their products exclusively, while 87 per cent back the widening and granting of patent term extensions to secondary formulations to reward incremental innovation. At present, an SPC can only be granted based on the first authorisation of a product, and the product must not previously have been the subject of an earlier granted SPC to the same applicant (i.e. one SPC per product per patentee only). A sizeable 93 per cent of respondents suggest that increasing incentives to reward R&D would help boost the appetite of investors in particular.

Scope of protection?

SPCs are available in all EU countries³, but are distinct from the underlying patent itself; an SPC is not simply a patent term extension. Protection given by an SPC is limited to the active ingredient(s) of

¹ Medicinal products are authorised in the EU under Directive 2001/83 (which replaced Directive 65/65) by the European Medicines Agency, in accordance with Council Regulation 726/2004 (which replaced the earlier Regulation 2309/93), or may be authorised nationally by equivalent national authorities.

² IMS Health (2000). SPCs worth millions to Pharma Companies in Europe, as cited in *IP Strategies in Fighting Generic Competition in the Pharmaceutical Industry*, Renee R Stadler, available at <http://www.bepress.com/ndsip/reports/art14/>.

³ and a few non-EU European countries, such as Norway and Switzerland.

69%

of respondents are satisfied that SPCs are consistently dealt with across Europe

an authorised medicinal product, to the extent that a so-called “basic patent” on which the SPC is based protects that product. Although there is a unified European framework setting out the SPC system (“the SPC regulation”⁴), separate SPC applications must be filed with the national patent offices of each jurisdiction. It is therefore possible that SPCs may be granted in some jurisdictions but not others; and indeed different patent offices interpret key parts of the regulation in different ways – although our research found that 69 per cent of industry was satisfied that SPCs were consistently dealt with across Europe.

However, over three-quarters (79 per cent) of industry participants would like to see protected not only the precise active ingredient, but also the underlying invention protected by the patent. In short, the same scope and protection should be offered in both cases.

This reveals one of the key tensions within the patent term extension system in Europe: that SPCs do not replicate the protection and scope provided by a patent. The regulation applies to the medical product itself and requires that it “be protected by” the basic patent. There is a line of case law that this is not the same question as whether sale of the product would infringe the basic patent, although the UK Court of Appeal has recently indicated that it intends to refer this question to the ECJ.

Combinations of products are the most obvious example. If a patent claims only product A, but a marketing authorisation has been granted for the combination A+B, then no SPC can be granted⁵ – although sale of A+B would infringe the patent, the patent is not considered to “protect” A+B. To some extent, this seems to come down to an assessment of what “invention” the patent is directed toward.

However, the UK at least has granted an SPC to a combination of tenofovir and emtricitabine, where the basic patent had a claim directed to a pharmaceutical composition comprising tenofovir “and optionally other therapeutic ingredients”⁶. This brief reference to combinations – together with a mention of combinations in the specification, and the general knowledge that antiretroviral treatments were often used in combination therapy – was held to be sufficient to allow the interpretation that the basic patent protected the combination, even in the absence of explicit disclosure of the particular combination. The lesson from this is clear – patent applications should be drafted with broad combination claims where possible.

SPC applications were refused in the UK⁷ where the patent was directed to a combination of the monoclonal antibody cetuximab and the anti-cancer agent irinotecan. Despite arguments to the contrary, the marketing authorisation was considered to be for cetuximab alone. The applications failed because (a) for the SPC for the combination, while the patents claimed the combination, the combination was not the subject of the approval and (b) on the second SPC for cetuximab alone, the patent only protected the combination. This illustrates the difficulty in ensuring that the patent protection aligns with what is ultimately approved as the medicinal product.

It is also possible to obtain an SPC directed to a combination of active products where separate SPCs have been granted to each product previously – for example, salmeterol and fluticasone have been the subject of SPCs in the UK separately and together⁸. Even enantiomers can be the subject of an SPC, if a previous marketing authorisation covers only the racemate, and the enantiomer has been separately authorised⁹.

However, the combination must be a combination of active ingredients. The ECJ ruled¹⁰ that a combination of carmustine (active) and proflupofen (an excipient allowing controlled release) in the product Gliadel[®] could not be the subject of an SPC because that combination could not be described as the product – the key being to identify the active ingredient. Further, in light of an earlier marketing authorisation for carmustine alone, an alternative application covering carmustine alone had to fail. Similarly, a combination of calcitriol with an ointment base (allowing a new therapeutic application) was refused SPC protection¹¹, as the only active ingredient was the previously-approved calcitriol itself.

⁴ Originally Council Regulation (EEC) 1768/92, since replaced by Council Regulation 469/2009. Also relevant is the plant protection products regulation, Council Regulation 1610/96. It should also be noted that Switzerland and Norway are outside the EU and so are not bound by the Regulation, but their SPC systems are broadly similar.

⁵ Takeda Chemical Industries SPC Applications (No. 3) [2003] EWHC 649 (Pat), [2004] RPC 37 (UK), where a patent to lansoprazole was not sufficient to allow grant of an SPC to a combination of lansoprazole in combination with an antibiotic. Similar decisions have come out of courts in Sweden, Denmark, Netherlands, and Germany.

⁶ Gilead Sciences, Inc.’s SPC Application [2008] EWHC 1902 (Pat).

⁷ SPC/GB04/037 and SPC/GB04/038. An SPC to cetuximab alone was refused as the patent did not protect this, while an SPC to cetuximab and irinotecan was refused as the marketing authorisation was not for this combination.

⁸ SPC/GB93/074 to salmeterol, SPC/GB93/075 to fluticasone, and SPC/GB99/016 to the combination.

⁹ Generics (UK) v Daiichi Pharmaceutical Co Ltd [2008] EWHC 2413 (Pat), [2009] EWCA Civ 646; similar decisions have come from Germany and the Netherlands.

¹⁰ Case 431/04 Massachusetts Institute of Technology v Deutsches Patentamt.

¹¹ Case 202/05 Yissum Research & Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents [2004] EWHC 2880.

87%

of respondents believe that the scope of extension granted by an SPC should be more flexible

Our survey found that a clear majority (87 per cent) believe that the scope of extension granted by an SPC should be more flexible, so as to reward further innovation in products which have previously received marketing authorisation. However, in view of the clear messages from the ECJ on this point, this seems unlikely to happen without legislative change.

National decisions from the Netherlands and France have further confirmed that vaccine adjuvants cannot be considered active ingredients, so SPC applications must fail if the active ingredient is merely presented in a new vaccine formulation. However, it appears that some patent offices have granted SPCs directed to vaccine adjuvants, so there may be some scope for protecting novel formulations.

In fact, vaccines present particular problems in respect of defining the product, since often the final product is a combination of distinct vaccines, or (in the case of seasonal flu vaccines) the product may change from season to season. The UK courts have held¹² that a patent to a vaccine based on a combination of two Bordetella pertussis antigens cannot be the basis for an SPC when the authorised product is a combination vaccine (Infanrix®, containing nine active ingredients to protect against diphtheria, tetanus, pertussis and poliomyelitis). The court in that case did recognise that it may be harsh to deprive SPC protection for polyvalent vaccines when their use is driven by public health policy but, nonetheless, the patent was held not to protect the product. On appeal, however, the court has since indicated that it intends to refer questions on this issue to the ECJ, so we may see clarity in this area.

Similar problems have been experienced in various countries when attempting to obtain SPCs for Gardasil® HPV vaccine – a polyvalent vaccine directed to multiple HPV strains. The

SPC applications were filed directed to individual strains, and refused on the basis that the authorisation was not directed to the product¹³. Again, these issues reflect the question of “protection” by a patent versus infringement of the patent. However, harmonisation in this area is also lacking, as it seems that SPCs have been granted in Austria, France, Italy, Sweden, and Switzerland for products specified as a single active ingredient where the authorised product contains multiple active ingredients. It follows that patentees should attempt to obtain patent protection closely aligned with what is likely to be marketed.

The EMEA has at least recognised that for pandemic outbreaks it is necessary to allow marketing authorisation of an initial “mock-up” strain, which is unlikely to be the actual strain when a pandemic outbreak occurs. This could cause problems in terms of SPC approval, if the patent offices did not recognise the need to cater for the possibility of the initial “mock-up” strain not being the actual pandemic strain. However, it appears that some national patent offices in Europe are flexible enough to allow a SPC product definition which is broad enough to cover future pandemic strains, which are not initially mentioned in the original marketing authorisation.

Similar unanswered questions accompany the definition of products for antibody therapies. Is it possible to obtain an SPC directed to the CDRs of an antibody, or using a functional definition? Would this cover third parties attempting to market biosimilar products? What about advanced cell and tissue therapies (likewise, how best to define a product – both for the marketing authorisation and for the SPC application – which is essentially a cell culture?) What about autologous cell therapies – can the product in these cases be clearly defined?

Who can file an SPC?

Only the patentee may obtain an SPC, and then only one SPC for each product. Where more than one patent is held which protects the product (for example, one patent directed to the product, and one patent directed to a medical use of that product), it is necessary to choose which to designate as the basic patent.

This choice should be based on considerations such as which offers the longest SPC term, which is potentially a stronger patent, and which may be easier to enforce (for example, it is generally easier to identify potential infringement of product patents than process patents). As a strategic matter, where there is a choice of patents to designate, SPC applications may be filed on more than one; assuming both applications are in order, the applicant may generally withdraw one to allow the other to go to grant. This may be particularly useful if one patent is under opposition at the EPO, and it is not clear whether it will survive with suitable scope to cover the product.

In the situation where a product is covered by separate patents held by separate patentees, then each patentee may obtain an SPC. Previously, it was necessary that a later SPC application be filed before the grant of any earlier SPCs (that is, all applications must be co-pending).

¹² *Medeva BV's SPC Applications*, [2010] EWHC 68 (Pat).

¹³ Note that an SPC has been granted for Gardasil®, directed to the specific combination of HPV strains in the vaccine.

87%

of respondents argue that SPCs should be expanded in scope to cover secondary medical formulations

However, important changes have been brought about by a recent ECJ ruling¹⁴ which held that this is no longer the case. It would not be just to deny a second SPC to a second patentee merely because they were unable to file an SPC application (for example, due to patent office delays) until after the grant of the first. Therefore, it is now possible to obtain an SPC despite an earlier granted SPC being held by another patentee. This is of key strategic importance, since it may allow the grant of an SPC on a later patent which was delayed in grant compared to those of competitors who have already obtained SPCs, so allowing longer term extension.

A basic patent may protect more than one product, in which case multiple SPCs may be obtained. For example, EP 0 451 216 B (PDL BioPharma) has claims directed to methods of humanising antibodies and describes in the experimental section humanised anti-IL2 antibodies. However, PDL has obtained SPCs on eight separate antibody products¹⁵, none of which is marketed by PDL¹⁶. It will be clear from this that there is no requirement that the applicant for the SPC has any connection with the medicinal product, other than that the product is protected by a basic patent. This provides further strategic opportunities for the astute patentee to prolong protection – and potential licence income – using SPCs.

When more than one marketing authorisation has been granted for the same product (for example, different formulations of the same active ingredient), only the first of these gives rise to the right to obtain an SPC. However, where the product is a combination of two active ingredients, there may be scope to rely on the more recent marketing approval granted in respect of the combination even where both products have

separately been subject to their own individual marketing authorisations.

When can an SPC be filed?

The regulation provides that an SPC application must be filed within six months of the date on which a marketing authorisation for the product was granted. If the authorisation is granted before the basic patent is granted, then the SPC must be filed within six months of the date of grant of the patent.

The term of the SPC is the delay between patent filing date and grant of the first marketing authorisation in the EU, less five years, to a maximum of five years.

A critical question is whether the “first marketing authorisation” means the first authorisation granted in accordance with Directive 2001/83 (or the earlier Directive 65/65), or an earlier authorisation granted under national law, which may not comply with the requirements of the Directive. This is of importance as there are a number of medicinal products which have been on the market under earlier legislation in countries prior to joining the EU – if the first marketing authorisation is taken as being the first authorisation granted in accordance with 2001/83, then this allows SPCs to be obtained for products which have already been on the market for some time.

Several cases¹⁷ on these lines have been referred to the Court of Justice of the European Union¹⁸; the outcome will again be of strategic importance to the industry, as it could provide a further way of extending protection for established products in certain markets.

As an SPC provides protection only if the time between patent application filing and marketing authorisation is more than five years, it may seem that there is no benefit in applying for an SPC if the delay is less than five years. However, a

¹⁴ C-482/07, *AHP Manufacturing BV v BIE*.

¹⁵ Zenapax®, Synagis®, Herceptin®, Avastin®, Xolair®, Tysabri®, Lucentis®, and Cimzia®.

¹⁶ In fact, the PDL patent was opposed at the EPO by 18 separate parties, including the marketers of these products. The opposition is still ongoing, despite the 20-year patent term expiring in December 2009.

¹⁷ Case C-427/09 *Generics (UK) Ltd v Synapttech Inc*; Case C-195/09 *Synthon BV v Merz Pharma GmbH & Co KG*.

¹⁸ The new name for the ECJ.

number of patentees have sought, and obtained, SPCs of zero or negative term¹⁹. Although this may seem somewhat pointless, there is a sound business reason for doing so. The EU has recently introduced a pediatric extension, which allows SPC holders to extend the term of their SPC for a further six months when an agreed pediatric investigation plan is established; this is intended to compensate for the costs in conducting pediatric clinical trials, rather than in delay for marketing authorisation, so is of a rather different category from the SPC itself. However, it has the consequence that a negative term SPC may grant positive protection when extended by six months.

At present, the UK and Netherlands have granted negative term SPCs, while Germany and Greece have refused such applications – but the German courts have referred the issue to the Court of Justice, which will provide clarity for patent holders.

Conclusion

Despite being intended to be a harmonised legal system – the SPC system is in fact still evolving and continues to present unanswered questions and fresh opportunities.

There is also the possibility for divergent decisions in different countries on a number of points, so it is essential to obtain local advice on any points where the boundaries of the SPC regulation are being tested. The pediatric extension provides scope for an additional six months extension, although here again the case law is still evolving and divergent. Applying for and obtaining an SPC is far from a mere formality, and it can be necessary to argue the case before the relevant patent offices.

What is inescapable is that SPCs are a powerful tool for the rights holder to prolong protection for a medicinal product at a time when that protection is likely to be most valuable. However, a degree of tactical skill is also necessary to ensure that the maximum reward is obtained.

¹⁹ For example, SPC/GB07/046 was granted in the UK to Merck and Co, Inc for sitagliptin, with a term of minus three months and 14 days.

79%

of respondents assert that SPCs ought to protect the underlying invention rather than simply the specific active product indicated by a patent

82%

of respondents believe that big pharma will be unable to innovate sufficiently from within to replenish the number of blockbusters going off-patent

3. Patenting strategy

Pharma companies are of course keen to see maximum return on their investment in research and development – and the emphasis from our research on the importance and scope of patent term extensions, and call for greater reward in the face of rising R&D costs, makes clear the pressures facing the industry. This is compounded by a still fragile global economic recovery.

Some 82 per cent of industry participants in our research argue that big pharma will simply be unable to innovate sufficiently from within to replenish the number of blockbusters going off-patent. As such, we can expect to see a combination of increased acquisitions and strategic partnerships on the one hand, and pressure to maximise the shelf-life of existing products on the other. On this latter point, drug repositioning is key.

Subject to the requirements of novelty and inventive step, the attractiveness of continuing to undertake research to reposition known drugs in the pharma market by, for example, finding new uses or reformulations and patenting these is unquestionable.

As first stated by EPO Biotech Appeal Board 3.3.4 in its Decision T1020/03 (Genentech / method of administration of IGF-1), they:

“could see no reason why the person who develops a novel therapy by looking for the most effective way in which a known composition can be administered should a priori be said to lack merit to such an extent that even the limited form of patent protection of the second medical use form can be denied without an examination of whether the therapy is indeed novel and inventive.”²⁰

Validity considerations

However, any expectation of a rush to make use of such re-positioning to extend useful patent coverage for a known therapeutic needs to be

tempered by the awareness that the normal requirements for patentability remain. For example, an alleged therapeutic use will not be considered new where it amounts to merely discovering more about the underlying mechanism of a known therapy.

Moreover, the English Court of Appeal has been at pains to point this out in the context of dismissing a validity attack against Merck’s European Patent on use of finasteride at novel dosages to treat baldness:

“...far from saying that in general specifying a new dosage regime in... a claim can give rise to a valid patent. On the contrary, nearly always such dosage regimes will be obvious – it is standard practice to investigate appropriate dosage regimes.”²¹

Nonetheless, this was a key decision in the UK and paves the way for the enforcement of second medical use dosing regime claims in the future.

Avoiding such grounds for obviousness requires showing that the dosage regime of concern is more than an arbitrary choice or mere predictive extrapolation of a workable range. On the EPO approach to inventive step, this demands presenting a problem and showing that the invention solves the problem. This involved reduced side-effects as considered in Decision T 1020/03, providing a new therapeutic purpose not previously considered viable as in the case of the above-noted Merck Patent, or a non-obvious improvement in efficacy.

This requirement points to the need for experimental evidence, which may be a tricky hurdle to surmount. The degree of evidence required equates with a plausibility test expounded by the EPO Appeal Board in Decision T 1329/04 (Johns Hopkins University / Growth differentiation factor-9), which is to at least make plausible to the person skilled in the art that the purported technical

²⁰ T1020/03 Reasons for Decision Para. 43.

²¹ Actavis UK Ltd v Merck & Co. Inc. [2008] EWCA Civ 444 (21 May 2008).

problem has indeed been solved²². In some circumstances, this may require even actual clinical trials.

Furthermore, the problem presented must be more than illusory. Changing formulation may well bring about a therapeutic benefit, but this will not suffice for patentability in the absence of a surprising effect if (a) such reformulation represents a common manner of formulation which was not precluded for the drug of concern and (b) the person skilled in the art would be confident that such formulation could be taken by humans and would have some therapeutic effect, albeit perhaps of lesser efficacy.

This was precisely the validity difficulty faced recently by Novartis in the English Court of Appeal when defending claims to sustained release formulation of fluvastatin, a well-known statin²³. The Appeal Court judges were keen to make clear that whether they adopted the EPO problem solution approach (PSA) or the approach to assessment of inventive step normally favoured by the English courts, the reformulation did not go hand in hand with any true basis for inventive step:

“Once the obstacle put forward in the Patent against being able to make a sustained release formulation was shown to be illusory, then a sustained release formulation is obvious... The PSA gives the same answer. What is the objective problem? Why that which the Patentee himself stated – to produce a sustained release form of fluvastatin. Was the solution obvious? Yes, any of the standard methods for such formulations would clearly work: there is no reason why they would not.”

As a contrast, reference was made to a recent consideration by the same Appeal Court of a sustained release form of oxycodone²⁴. The slow release form transformed it from a weak opioid generally administered as

a co-drug to a serious alternative to morphine. This was held to be wholly unexpected and hence good basis for a finding of non-obviousness.

Claims to an actual new use for a novel indication must equally be supported by convincing experimental evidence of a solution to a problem. Where prior art indicators, even in certain circumstances in vitro experiments, can be alleged to provide motivation to further investigate a therapeutic use, again the proffered problem can be held in effect to be illusory.

In such an instance, EPO Biotech Appeal Board 3.3.4 has substituted the PSA with the “*try and see approach*” and so held lack of inventive step. Thus in their Decision T 1045/98 (Schering / Antagonist to interleukin-5 for preventing or reducing eosinophilia), the Board considered in vivo experiments in mice against the prior art background of in vitro studies on the causation of eosinophilia and commented:

“Although knowing that in vitro experiments cannot mimic the in vivo setting, the skilled person would have perceived the experiments reported... as being encouraging. Thus in spite of the understandable uncertainties which also characterise biological experiments, the skilled person had no reasons to adopt a sceptical attitude. He or she would have had either some expectations of success or, at worst, no particular expectations of any sort, but only a “try and see” attitude, which... does not equate with an absence of reasonable expectation of success.”²⁵

In view of these legal developments relating to secondary formulations, it is interesting to note that barely half (54 per cent) of industry participants in our research felt that the European system was becoming more favourable toward secondary, follow-on patents. This suggests that although recent

²² Headnote EPO Appeal Board Decision T 1329/04-3.3.8.

²³ *Actavis UK Ltd v Novartis AG* [2010] EWCA Civ 82 (17th February 2010).

²⁴ *Napp v Ratiopharm* [2009] EWCA Civ 252; [2009] RPC 539.

²⁵ T 1045/98 *Reasons for Decision Para. 17.*

decisions confirm that protection may be available in some cases, demonstrating the required novelty and inventive step is still a burden.

However, respondents were decisive in confirming that secondary patents are themselves essential to the wellbeing of the industry – with 83 per cent arguing that a system that failed to protect secondary, follow-on developments would not be able to provide the protection needed to make such innovation commercially worthwhile. Over three-quarters (78 per cent) suggested critics of follow-on drug development failed to give sufficient recognition to the role incremental innovation plays in advancing medicine.

The bar for originators is certainly high. And while repositioning of a drug in the pharma market can provide valuable extension of patent coverage, this demands careful timing to ensure the right experimental support while avoiding the potential prior art pitfalls.

New EPO practice

Recent changes at the EPO will mean that patenting strategy also needs to change. The new divisional and search practice at the EPO brought into full operation from 1st April 2010 provides pitfalls for the unwary seeking to gain patent protection for medical uses.

It needs to be kept in mind that the EPO will only carry out one search in respect of an application, which may be the international search in respect of an international patent application filing under the Patent Cooperation Treaty (PCT). A problem arises if a broad claim is held to lack unity, e.g. a posteriori on the basis of cited prior art documents, and covers various medical uses, especially if not all are fully supported.

The claims must be restricted to the searched subject matter for examination and further inventions

transferred to one or more divisionals²⁶. Any such divisional must be on file at the latest by 24 months from the first examination report from the EPO examining division raising lack of unity²⁷, i.e. the first examination report in the European regional phase where the PCT route is used.

In short, the days are gone when an initial patent application, either filed direct at the EPO or a PCT application designating the EPO, might be continually dipped into for more inventions over a long period of time with only regard to at least one corresponding European application remaining pending. Moreover, if the “wrong” subject matter is searched by the EPO in an international phase, there is no longer any possibility of swapping inventions for examination in the European regional phase.

As well as these changes, the manner of claiming new uses of known drugs has to radically alter in light of the recent EPO Enlarged Board Decision G2/08, which finally put an end to the traditional so-called “Swiss-form” use claim at the EPO for coverage of any further medical use of a known therapeutic. The Swiss-form claim was expressed as follows:

“Use of [known substance or composition] in the manufacture of a medicament for the treatment of [a disease]”

Now, the form of claim to be used in such a situation is exclusively that permitted by Article 54(5) of EPC 2000²⁸. Whether a first or further medical use of a known compound is to be claimed, the form of claim to be used at the EPO is:

[Known substance or composition for use in [new therapeutic use]

This change is more than semantic. Such a claim is not only simpler to write, but also simpler to enforce. “The limited form of patent protection of the second medical use form” – alluded to by EPO Biotech Appeal Board 3.3.4 in its Decision

78%

of respondents claim that critics of follow-on drug development fail to give sufficient recognition to the role incremental innovation plays in advancing medicine

²⁶ Rule 164 EPC.

²⁷ Deadline extended to 1st October 2010 for applications for which 24 months has already expired or will expire before 1st October 2010; Decision of the Administrative Council of 25th March 2009 amending the Implementing Regulations of the EPC introducing new Rule 36(1)(a). If no lack of unity objection is raised in an examination report, the divisional deadline is 24 months from the first examination report on the earliest EPO case in a family.

²⁸ Subject to the 3 month amnesty permitted by the EPO Enlarged Board based on priority date from publication of the decision in the Official Journal of the EPO.

82%

of respondents think that the EPO rule changes introduced in April 2010 are likely to be a burden on smaller companies

T1020/03 – is made rather less limited by no longer needing to rely on indirect infringement of a Swiss-form use claim. Rather, the “for use” format opens up the possibility of direct infringement by manufacturers and importers as well as purchasers such as health authorities.

The future

So how should life sciences companies approach these changes at the EPO? Where the problem of the “wrong” invention having been searched in the international phase applies, the best solution appears to be to carry out European regional phase entry prior to the 31-month deadline for doing so, paying only the relatively low filing fee, and to file a divisional prior to the 31-month deadline in order to secure a new EPO supplementary search. The parent case will be considered to be abandoned due to non-payment of the designation and examination fees. If it is too late to do this, regional phase entry may be effected at the 31-month deadline, but all relevant fees will need to be paid on the parent case in order to validly obtain a pending parent case. Where such early divisionals are filed, request for accelerated search may be a useful option to take up; this requires no official fee payment or reason to be given.

Lack of experimental evidence rendering a claimed use at least plausible in the eyes of the EPO cannot be rectified post-filing.²⁹ The problem is exacerbated by the shortened timetable for divisional filings – if numerous therapeutic applications are suggested in an initial application, the deadline for divisional filings may well expire before sufficient evidence can be amassed to demonstrate the commercial value of pursuing protection for these indications. Hence, there is now a strong incentive provided by the EPO

not to claim ‘over broadly’, but rather to tailor claims to the experimental support.

For those applicants of a PCT application (i.e. having the option of an international search at a patent office other than the EPO, such as the USPTO), the option still remains of swapping inventions for search by the EPO at entry to the European regional phase. Hence, where multiple medical uses are covered, there may be benefit in not having the EPO carry out the international search. Given the new EPO requirement to respond to any objections raised in any international search report and written opinion prepared by the EPO shortly after regional phase entry, there may be further incentive for obtaining an international search from a non-EPO searching authority.

Moreover, in view of the cost and time restraint at the EPO on divisional filing, there may be instances where risk versus benefit analysis lies in not bundling all new uses into a single application but considering a rolling program of narrower filings aimed at closely aligning the initial filing with the availability of supporting experimental data and commercial priority.

The changes at the EPO are viewed with caution by respondents to our survey. While 55 per cent are in favour of a swifter patent grant process – which the changes are seeking to deliver – 86 per cent felt it essential for the industry that the European patenting process did not become more labour-intensive. 82 per cent thought it likely that forcing companies to make early decisions that affect the scope of protection covering their R&D would be a likely burden on smaller companies. In view of their limited resource and the fact that tomorrow’s innovation is likely to be staged mainly amongst smaller biotechs, this is a sizeable concern. 81 per cent suggested

²⁹ T 1329/04 applies.

Conclusion

making patent applications more laborious could discourage inventors further and widen the ‘innovation gap’ with the US, where the record for commercialising R&D among non-corporates is already much higher.

As far as pursuing infringement is concerned, the new “for use” form of second medical use claim will make it simpler to enforce. Undeniably, the research exemption and “EU Bolar-like provision”³⁰ will continue to provide some limited relief from infringement in relation to those carrying out certain clinical trials. However, in Europe, the extent of those defences varies greatly on a country-by-country basis and care will need to be taken. It is clear that the days are over when some in the pharma industry might allege that claims in Europe covering a second or further medical use are ‘second best’ in building a protective wall around their products. The increased ease of enforcing second medical ‘for use’ claims, including against generic manufacturers (either as direct infringers or joint tortfeasors), is evident.

This adds to the desirability of looking for patenting opportunities to extend patent coverage life through improvements in administration regime and/or new uses. A possibility for avoiding a finding of contributory infringement may still arise where the drug of concern is readily available but, in reality, such risk may well be *de minimis*, especially if a new formulation or delivery system is involved or the drug of concern is a complex biologic.

Re-examining known compounds for novel therapeutic benefits can provide useful claims with ability to frustrate generic manufacturers but, for this to be so, it is important to ensure that claims are closely aligned with experimental evidence supporting true invention. Trying to claim too much too soon has evident potential dangers.

It is clear that the biotech and pharmaceutical industries are undergoing a degree of convergence, and indeed that this is necessary to address the problems caused by imminent patent expiries and narrowing pipelines for future drug development. Both industries can adopt similar tactics to find solutions to their problems.

Other than identifying new therapeutic molecules – whether traditional NCEs or novel biotherapeutics – a key approach has to be to ensure a fair scope of protection is obtained in return for investment in R&D. Our report here discusses a number of issues in adopting that approach, including obtaining patent term extensions, and secondary patenting strategies. However, there are of course pitfalls, such as the increased scrutiny of competition authorities, and the difficulties of ensuring that the available protection aligns with the commercial product.

The responses to our research emphasised that protection for innovation is essential for the future of drug development, and that innovation could be found in all aspects of the drug development process, whether early-stage lead development, or later identification of new uses for known drugs. The narrowing focus of personalised medicine too will mean that obtaining a fair protection for the investment is more important in future.

On the whole, it is heartening that many respondents to our industry survey and users of the system believe that there are certain aspects of the current system which work well. However, there are clear areas for possible improvement which would be seen as investing in innovation.

For example, this could include extending the current SPC system in Europe to ensure that the scope of protection corresponds with that given by the patent, or moving towards a truly harmonised European patent and litigation system. Without these and other changes, there is a fear that the gap in securing and exploiting innovation between the US and Europe may grow, and that the future innovations in medicine needed to promote health may be compromised.

³⁰ EU Directive 2004/27.

Annex – Patent term extensions worldwide

Country	Extension of Patent Term	Type of Products	Deadline	Can you get more than one extension per patent/product	Paediatric extensions
Australia	Yes, maximum of 5 years. Calculated as period of delay from patent filing to regulatory approval, less 5 years.	Pharmaceutical substance per se or process, of production using DNA technology. Not methods of manufacture or uses.	Within 6 months of patent grant or entry into Register of Therapeutic goods, whichever is later.	Only one extension.	No.
Canada	No.	-	-	-	-
China	No.	-	-	-	-
EU	Yes, but to product, maximum of 5 years. Calculated as period of delay from patent filing to regulatory approval, less 5 years. Total product protection not to exceed 15 years.	Pharmaceutical, veterinary products, pesticide/herbicide, methods of production or uses.	Within 6 months of grant of the marketing authority or 6 month of patent grant whichever is later.	More than one SPC extension per patent possible for different products.	Yes – 6 months only if SPC granted.
India	No.	-	-	-	-
Israel	Yes. Maximum of 5 years but tied to other countries extension terms and minimum applied. Total patent protection not to exceed 14 years. If applied for, but not granted in US, no allowed grant in Israel.	Pharmaceuticals and veterinary products and medical devices. Methods and uses also protected.	Within 90 days of marketing authorisation.	Only one extension per product.	No.
Japan	Maximum 5 year extension from end of patent term.	Pharmaceuticals, agrochemicals, veterinary products.	Within 3 months of MA or must apply within 6 months of end of patent term.	More than one extension provided to a different product. Possibly more than one extension available for each active ingredient.	No.

Country	Extension of Patent Term	Type of Products	Deadline	Can you get more than one extension per patent/product	Paediatric extensions
New Zealand	No	-	-	-	-
Russia	Yes	Pharmaceutical, pesticide or agrochemical. Not to be based on methods or use.	Within 6 months of grant of the marketing authority or 6 month of patent grant whichever is later.	More than one patent can be extended based on a single MA.	No.
Singapore	Yes – if more than 2 years of a delay in obtaining marketing authorisation. Although normally granted on basis of foreign marketing authorisation and so quite rare to get such a delay.	Pharmaceuticals including traditional medicines and homeopathic medicines.	6 month of MA or patent grant which ever is later.	Not clear due to lack of case law.	No.
South Korea	Yes, if more than 2 year delay, obtaining regulatory approval.	Pharmaceuticals, processes and uses not cosmetics, food additives, medical instruments, or pharmaceutical intermediates.	Within 3 months of regulatory approval, not within last 6 months of patent term.	One extension per patent even where multiple authorisations obtained. Multiple patents can be extended based on one authorisation.	-
Taiwan	Yes, if more than 2 years of a delay obtaining regulatory approval.	Pharmaceutical, pesticide or methods of production.	Within 3 months of regulatory approval.	Only one extension per patent.	No.
USA	Yes up to 5 years, maximum term of patent protection not to exceed 14 years. Period of extension=1/2 (testing phase) + approval phase	Human or veterinary product, including combination products, medical devices, as well as methods of manufacture.	Within 60 days of regulatory approval.	Can only extend patent once	Yes – 6 months not tied to patent term authorisation.

Marks & Clerk contacts

If you would like more information about the survey or this report, contact the lead authors from our bioscience group.



Dr Paul Chapman
Partner, European Patent Attorney
Marks & Clerk LLP
Edinburgh Office
T: +44 (0)131 221 7000
E: pchapman@marks-clerk.com

Dr Gareth Williams
Partner, European Patent Attorney
Marks & Clerk LLP
Cambridge Office
T: +44 (0)1223 345520
E: gwilliams@marks-clerk.com



Dr Claire Irvine
Partner, European Patent Attorney
Marks & Clerk LLP
Oxford Office
T: +44 (0)1865 397900
E: cirvine@marks-clerk.com

Mike Gilbert
Partner, Solicitor
Marks & Clerk Solicitors LLP
London Office
T: +44 (0)20 7420 0250
E: mgilbert@marks-clerk.com

About Marks & Clerk

The Marks & Clerk group is a world leader in intellectual property. Clients and peers worldwide have nominated us for many awards and we consistently achieve top rankings in major legal directories and IP surveys.

Our patent attorneys, trade mark attorneys and solicitors offer a comprehensive range of services covering patents, trade marks, designs and copyright. This includes obtaining protection worldwide, portfolio management, strategic and commercial advice, licensing, enforcement, due diligence and litigation. The extent of our resources – with some 600 people worldwide – means we are able to offer expertise covering an exceptionally diverse range of technologies and commercial sectors.

Working in partnership with our clients, we are committed to understanding their business requirements and building strong, long-term relationships. Our size and structure enables us to tailor our services and put forward the best individuals or teams for each client with local access to the whole strength and depth of Marks & Clerk.

With an expanding network of offices in the UK (11 locations), Europe, Asia and North America, and long-established relationships with other trusted IP firms worldwide, we are able to provide a consistently high quality and cost-effective service locally and globally.

www.marks-clerk.com

