Round Table: Biotech & Pharmaceutical

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Born in Lisbon. Law degree and postgraduate studies in international commercial law and arbitration at the Faculty of Law, University of Lisbon.

Member of the Portuguese Bar Association since 2000, he joined the firm in 1998. His main areas of practice are employment law, pharmaceutical law, commercial law and international contracts, corporate and M&A, and civil law. He is repeatedly distinguished in the Portuguese rankings of worldwide publications for his activity in the fields of employment law, pharmacetical law and commercial law.

Under Goncalo Pinto Ferreira management the Pharmaceutical Law and Life Sciences Department of the firm acts as legal advisor to a number of Portuguese and international clients, including some of the main international pharmaceutical and medical devices manufacturers operating in Portugal, as well as regarding legal innovations in pharmacetical law, such as pharmacovigilance and pharmaceutical liability, and the developing field of Biotechnology.

He is heavily engaged also in Compliance related matters, notably by being member of Compliance Committees in the Pharmaceutical and Medical Devices field.

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Beatriz Cinco is a lawyer in the Pharmaceutical & Healthcare practice Uria Menendez. She joined the firm in 2001 and was appointed Counsel in January 2013.

She advises national and multinational companies in the pharmaceutical, healthcare and food sectors on all contractual, commercial and regulatory aspects of their businesses. Ms Cinco specialises in distribution policies, commercial agreements, R&D, pricing and reimbursement of medicines and medical devices, compliance, and promotional activities. She also represents clients before administrative and contentious administrative courts in regulatory matters.

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Bonella Ramsay is co-chair of DLA Piper’s Global Life Sciences Sector. Her practice is focused on international IP, transactional and regulatory matters for biopharma and med. tech. companies. She advises clients across the product life cycle on in/out-licensing deals, strategic alliances, spin-outs, R&D collaborations, roll-out of multi-jurisdictional clinical trial programmes, manufacturing and supply chain arrangements, promotion and market access issues. Bonella also has experience in advising on business process outsourcing/off-shoring projects for life sciences clients including in relation to IT/IS services, clinical services, clinical data processing, drug safety and other key regulatory-driven functions. Bonella is highlighted as a leading individual in IP in Legal Experts 2012.

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Dr. Despina Samara specialises in EU and Greek pharmaceutical law and regulation, with particular emphasis on pharmaceutical antitrust as well as general EU law. She advises and assists clients of the pharmaceutical industry in everyday matters while she has extensive experience in representing them in procedures, before both national and community authorities and courts. Dr. Samara has also completed a stage with the Industrial Property Unit of the Directorate General of Internal Market, European Commission when reviewing the compulsory licensing directive back in 2005. She is a regular contributor in experts’ publications on pharmaceutical legal matters.

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Gregory K. Bell, PhD, is a group vice president and global leader of the Life Sciences practice at Charles River Associates. Charles River Associates is a leading global consulting firm that offers business, financial, and economic consulting services to industry, government, and financial clients. Maximizing product value and corporate performance, CRA consultants combine knowledge and experience with state-of-the-art analytical tools and methodologies tailored to client-specific needs. The Life Sciences practice provides strategic consulting services, policy advice, and damages and economics expertise in litigation disputes within the life sciences industries, covering pharmaceuticals, biotechnology, medical devices, diagnostics, and consumer products.

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Gary’s practice extends across the following areas in biotechnology and pharmaceuticals:
- advice towards strategic IP development in start-up companies and SMEs;
- drafting patent applications;
- prosecution of patent applications;
- opinion work, including freedom to operate opinions, opinions for regulatory approval of pharmaceuticals as well as general due diligence opinion; and
- contentious matters including oppositions and court actions (infringement and revocation actions) in Australia and New Zealand.

Some leading cases that Gary has acted in are:
1. Genetics Institute Inc v Kirin-Amgen Inc (1996) 34 FPR 513 (Acted for Kirin Amgen);
2. Pharo Overseas Pharmaceuticals v Eli Lilly and Co (2005) 225 ALR 416 (Acted for Eli Lilly and Co);
3. Genentech, Inc v Ludwig Institute for Cancer Research and Human Genome Sciences, Inc [2006] APO 20 (5 June 2006) (Acted for Human Genome Sciences Inc); and

Outside patent litigation, he handles a range of other IP litigation and helps clients with transactional work.

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Janet worked with a wide range of clients but has particular expertise within the life sciences industry and in working with educational institutions and their spin-out companies.

Janet's life sciences work covers commercial life sciences transactions including their regulatory and IP implications. Her work ranges from early R&D phases and, clinical trials to licensing, manufacturing and supply and beyond. Her experience includes advising on: clinical trials agreements and related CRO agreements; in-licensing, dossier and associated brand acquisitions; and companion diagnostic transactions. Chambers UK independently rates Janet for life sciences nationally as being respected for her ability to see solutions quickly and effectively.

In Legal 500's review of education sector legal advice she has scored a perfect 10. Janet has presented on many occasions for both AURIL (Aso-

Janet is a regular speaker and commentator on life sciences and education IP matters (including for PraxiusOne on Research Contracts, IP Licensing and Spin Out Companies) and has written for Pharma Law. She is also recommended by the IAM 250s the Worlds Leading Patent & Technology Lawyers 2012/2013.

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Janet qualified as a solicitor in 1983. She deals with the full range of IP rights, from patents to trade marks. She specialises particularly in IP transactions in the science and technology fields and their anti-trust issues. Janet is one of a limited number of UK IP licensing professionals recommended by the international guide IAM 1000 - Guide to the Worlds Pat-

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tative focus on physicians is coming under increasing scrutiny. As a result, we are seeing more opportunities and companies emerge around different models of engaging the consumer and the physician across the wellness and health continuum. For pharmaceutical companies, their opportunity space is expanding as we continue to migrate from the blockbuster model to one where the focus is more on a range of products and partner alliances that span the spectrum of a disease or therapeutic condition, from prevention through cure or maintenance.

Ferreira: The healthcare industry is facing a particularly difficult market environment, which is mainly focused in austerity and cost pressures. As a consequence, in the last couple of years we see a significant change of the landscape of the pharmaceutical companies, especially, as consolidations of the last decades have resulted in companies of incredible scale and thus, incredible costs of labour. Across the industry, due to the need for major restructuring initiatives to adapt to this new environment, pharmaceutical companies have been closing manufacturing plants, laboratories and eliminating sales units. This means that pharmaceutical companies need to address the way “remaining” people work more efficiently. Efficiency gains can come out of people with great experience and input working together to foresee problems, proactively mitigate risks or minimise losses.

Hade: The Life Sciences sector has undergone significant transformation in recent years. For larger companies in the sector, these changes have been driven by the loss of exclusivity on blockbuster drugs, diminished research pipelines, and increased competition for market and health care payment shares. Smaller companies have faced their own challenges, including scarcity of investment dollars and repositioning of research funding. 2013 should provide opportunities for the small to mid-size companies to engage in M&A activity with large-pharma as an alternative to traditional fund raising means (e.g., venture capital, debt financing, IPO).

Lipkus: There is certainly a paradigm shift away from early-stage innovation, but I view it as a strategic shift that some companies are taking rather than a wholesale industry shift. Some large companies have observed that they are much better at commercialising than inventing. Thank Pfizer, Eli Lilly, Astrazeneca and Merck. These companies are actively seeking external inventions that they can commercialise, both in established markets and emerging ones. Small and mid-market companies can take advantage of this large-pharma strategy by inventing with a view to licensing "turnkey" products to these large companies.

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Knowles: A number of factors have combined together to make it increasingly difficult for Big Pharma to continue to deliver "blockbuster" products:

- There are very few "easy" and predictable therapeutic targets remaining. Therefore, the probability of success of a drug discovery and clinical program has reduced.
- Deep advances in preclinical and predictive science, it remains very difficult to reliably predict clinical outcomes. As a result, the only way to reliably test safety and efficacy is to complete extremely expensive clinical trials. The failure rate of trials remains stubbornly high. Until the science catches up, development will remain expensive and risky.
- Many of the established markets are facing increasing demands on their healthcare budgets. This has resulted in new drugs not only having to show safety and efficacy for regulatory approval, but also to demonstrate positive health economics over and above existing therapies. There are many examples of bodies such as NICE in the UK rejecting approved drugs because they are deemed not to meet cost benefit requirements.

Arrieta: This is a very complex phenomenon; there is no single answer to this question, and the reasons vary from country to country, from company to company, and from product to product. As regards our jurisdiction (Spain), and many others in Europe, an increasing concern is the reduction of effective patent life in pharmaceuticals, not only due to the increasingly long periods required for development and marketing authorisations, but also due to the delays in the launch of new drugs as a result of demanding pricing and reimbursement procedures. There is ample room for improvement to try to avoid a duplication of the evaluation processes, by coordinating assessment methodologies used in the marketing authorisation decision and the pricing and reimbursement decision.

4. How can the pharmaceutical industry adapt and change in order to survive? What effective business models currently exist?

Bell: There are almost as many business models as there are pharmaceutical companies. Today, there may be more biotechnology start-ups than ever before, and that trend will continue as technology continues to uncover new product opportunities. These companies tend to focus on development, advancing their product concept to the stage where it could be out-licensed to the company could partner with a larger, established organisation to bring the product to the pharmaceutical space, perhaps in a specific therapeutic area, either with or without their own research and development capabilities. Other large pharmaceutical companies are taking more advantage of their breadth and the blurring lines among pharmaceuticals, devices, diagnostics, and the over-the-counter products to provide a suite of products and services that span greater segments of the health and wellness continuum.

Ferreira: Despite the difficulties, the market is already showing that efficient adaptation capacity is allowing some players to better react...
Arrieta: Pharmaceutical companies must do business in an extremely regulated environment, where strategic, long-term decisions are
injuring projects with multiple third parties (e.g. universities, biotechs etc.) or participating in schemes offering access to a pool of resources unmet medical need. We also expect to see increasing recourse to open innovation, whether by way of offering for tender and conduct-
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Kashyap: there are good examples of open innovation collaborations with both competitors and academic institutions;
out the door. The latter strategy has been successful in other industries, but it remains to be seen how multiple companies taking a
similar approach will fare.

Ramsay: The industry has responded to the business opportunities and challenges in various ways, including:
• Heavy M&A activity, resulting in both dramatic consolidations and divestitures;
• Therapeutic specialisation and the trimming of R&D portfolios;
• Shedding of non-core assets;
• Proliferation of in/out-licensing and alliances;
• Large-pharma stepping in to fill the biotech investor gap;
• Outsourcing of functions, including R&D, clinical trials and sales;
• Deep cost cutting across the board.
Increasing their presence in emerging markets and, in the case of many innovators, growing their established product portfolios.
Further business models changes are needed to fully embrace the era of personalised medical big data, big and increased transparency
requirements.

Haile: The pharmaceutical industry will need to continue with the consolidation we have seen in recent years, including the ‘megamergers’ like
Glaxo/Novartis (2009), Sanofi/Genezyme (2011), Teva/Nycomed (2011), Roche/Gentech (2009), Pfizer/Wyeth (2009) and Merck/Scher-
ing Plough (2009), to name a few. Although companies like Merck and 86 continue to operate with large portfolios of consumer and
non-pharmaceutical businesses, others members of the sector are shedding businesses or undergoing major restructuring.
Divestiture has become a more common occurrence with the pharma industry in recent years. Pfizer, for example, sold off its infant formula and
animal health businesses. Abbott announced in January 2013 that it would split into two companies: one focused on its proprietary
biopharma business (ABBVie), the other to include its medical device, consumer health care and generic businesses.

Lipkus: I see three successful strategic models in operation right now: proprietary discovery, geographic expansion, and leveraged inno-
vation. The proprietary discovery model has allowed some companies (e.g. Vertex) to identify disease targets that may not be discernible
from the literature – better scientific modelling increases the chances of success for a drug candidate. Geographic expansion appears to be
the preferred short-term model for companies going over the patent cliff – market expansion into emerging markets has provided some
cushion for the fall and enabled the companies to expand access to essential medicines. The leveraged innovation model is the big
bet of several large companies – it involves opening the door to external innovation and hope that exciting drug candidates will come
through the door. The latter strategy has been successful in other industries, but it remains to be seen how multiple companies taking a
similar approach will fare.

Knowles: Big Pharma will need to remain innovative to survive in the long term. This will mean adopting new ways of operating and
doing business including changing the culture of “owning everything” to “owning a part” of an asset. For example:
• there are good examples of open innovation collaborations with both competitors and academic institutions;
• increased transparency and the pooling of data to enable better understanding of disease and the identification of new targets;
• Big Pharma partnering on drug development/commercialisation to capitalise on synergies and expertise in specific diseases/sectors.

It is likely that Western pharma companies will continue to invest in emerging markets to access the growth that is promised as popula-
tions in those countries start to demand modern therapies and also to access emerging scientific talent.

Kashyap: Traditionally the pharma companies have alone pursued R&D and commercialising of their products. However, in future this
model will evolve as both innovator and generics companies will need to improve their R&D, reduce their costs, tap emerging markets, compete with each other (innovator vs. generic), face challenge from biosimilars and be patient centric. Thus the current effective busi-
ess models involve where the pharma industry need to go beyond their existing niche, to become more patient centric, collaborate with public organisations, collaborate to outsource and/or offshore expensive business processes to develop effective new medicines more economically and ensure such products and services really make a difference to patients.

Parker: Strategies employed by pharmaceutical companies to deal with the pressures of having to deliver cost-effective but therapeuti-
ically and pharmaceutically innovative drugs include the development of competitiveness models, with a view to fostering entrepreneur-
ial drive and prioritising (at the stage of development) the most promising R&D projects and targeting therapeutic areas with high
unmet medical need. We also expect to see increasing recourse to open innovation, whether by way of offering for tender and conduct-
ing projects with multiple third parties (e.g. universities, biotechs etc.) or participating in schemes offering access to a pool of resources (e.g. patent pools).

Arrita: Pharmaceutical companies must do business in an extremely regulated environment, where strategic, long-term decisions are
significantly, and many times abruptly, affected by legal and government measures. In the past few years, pharmaceutical expenditure has
been one of the main areas affected by government cost-containment measures in Spain. Still, there are areas where regulations in force still
leave some margin for commercial freedom and where some companies have implemented policies aimed at trying to rationalise and gain efficacies. There have been interesting developments in Spain concerning the use of the freedom to set prices in the (limited) areas not affected by government intervention. In fact, the Spanish regulations have been
recently amended to further reduce the scope of government pricing intervention and generally limit it only to medicines actually reim-
bursed by the state; this, no doubt, represents a very interesting opportunity (although it involves great practical complexity).

5. Discuss the importance of staying on top of emerging science as well as new products and services? Are there any interesting develop-
ments which we should keep an eye on?

Haile: Personalised Medicine will continue to be in the forefront in 2013 and beyond. Historically, private insurers would rarely reimburse
for genetic tests, thus, new policies and government-funded medical care issues need to be addressed. There are also significant ethical and
disclosure implications with sequencing of our genomes. Getting sequenced could subject people to genetic discrimination for things like
life and disability insurance. We are clearly entering an era of unprecedented self-knowledge. We are really beginning to come to under-
stand that we can begin to take steps to take control of our own future. Genomics offers the chance to look, in the most precise way, at
what the causes of illness are and how to prevent and treat illnesses with that information. Whereas personalised medicine in the recent past was ‘reactive’ and based on analysing the genetic basis for an already diagnosed disease (e.g., tumours), personal genomics provides the opportunity to be ‘proactive’, and look at our overall genetic make-up in ways we could not have imagined even a decade ago.

Lipkus: Biological Big Data is about to become big business. Only recently have we started to see integration between bioinformatics, bi-
chemistry and molecular biology. We are seeing a convergence of science and business software: scientists are developing better ways to
model biological interactions, and computers are getting better at carrying out the complex processes required to provide meaningful in-
formation about drug candidates. The result is a new industry geared toward assisting drug companies to determine whether their drug candi-
dates will be successful before the first in vitro test is carried out. These new in silico tools will revolutionise how companies screen products
and will inform the approaches that drug regulators take in evaluating drugs in the coming years.

Knowles: It is becoming clear that personalised healthcare will continue to become increasingly important aspect of modern medicine.
Being able to select patients such that they receive the right drug at the right dose is obviously important for drugs which are already on the market.
However, patient selection is also going to feature more in the development of new drugs. Being able to prospectively select patient populations in clinical trials with a higher probability of responding to treatment has the potential to significantly de-risk expensive clinical trials and provide more approved products.

However, there have been recent developments, particularly in the US, where it is becoming more challenging for innovators to protect IP in this area. The outcome of the Mythirias and Prometheus court decisions could have a significant impact on investment and hence the speed of development of this exciting field.

Kashyap: The emerging science in healthcare is now becoming patient centric by evolving a customised healthcare system. Thus pharma
and biotech industry will need to restructure their healthcare services in becoming more patient centric. Going forward the drug develop-
ment may not be an isolated process of drug discovery per se against disease/disorder but an integrated healthcare progression based on (i)
derstanding disease etiology; (ii) identifying and developing patient centric biomarkers against the disease; (iii) identifying and develop-
ing drug for the right course of treatment/medication; and (v) maybe personalised safety standards for medication for patient.

Arrita: In Spain, once a generic product enters the market, the originator company not only suffers an immediate impact on price (as the
originator price is automatically reduced to the cheapest generic price, and there are other aggressive competition dynamics). Spanish
legislation also generally provides that generics are the first choice for INN prescriptions and dispensations (which is the general rule) when
the generic and the originator have the same price. No doubt, originator companies suffer a significant competitive disadvantage versus
generic companies as a result of these rules, which makes the ability to launch innovative, patented products protected crucial. There is cur-
rently a delay of 30 days in Spain concerning the review of the criteria and decision-making process for the reimbursement and price fixing
of new products. A new draft Royal Decree (aimed at replacing current regulations dating from 1990) is expected to be issued for consultation
in the next few weeks. There are, as yet, not many indications as to which changes will be implemented but the main purpose of the review is
the “selective reimbursement” principle and to avoid duplicity of efficacy and safety reviews by different stakeholders in the healthcare field (and, mainly, by the different regions – or even different hospitals - in Spain).

6. How do you analyse the level of risk in drug development stage? What risk management and accountability procedures would you imple-
ment in order to safeguard a company from litigation?

Haile: Compliance and Transparency have been and will continue to be key issues for global pharma companies in 2013. There has been
and continues to be emerging legislation worldwide to prevent corruption and increase transparency within the industry. The legislation
aims at regulating business practices, and the interpretation of the rules and cases of corruption and the impact of the new regulations on
investigations/wistleblowers; issues under the Anti Bribery Act in the UK, Foreign Corrupt Practices Act (FCPA), the OECD Convention
and the Sunshine Act therefore companies will need to ensure they have strict risk and compliance programs in place to avoid litigation in
the future.
Watts: From a lawyer’s perspective, analysing risk goes hand-in-hand with whether the company is following its own procedures. It’s vital that protocols for drug development programs are followed to the letter and that you are auditing on a regular basis. Companies need their in-house legal team involved from an early stage in drug development, educating employees on the need for compliance with protocols and vigilance in record keeping. This will help prevent mistakes that can result in recalls. 

Parker: In the current cost-conscious environment, pharmaceutical companies are making increasing use of lower cost jurisdictions, which may also offer a larger potential patient population, to conduct their clinical development. However, with this trend come increased compliance concerns, not only from a pharmaceutical regulatory perspective but also in terms of corporate compliance issues (e.g. anti-brush legislation with extra-territorial effect). As a result, careful vetting of third party service providers (e.g. CROs) and the contractual imposition (and auditing) of strict compliance protocols has become increasingly important. 

When deciding where to conduct clinical trials companies need to consider also the patent infringement risk, which varies significantly from country to country as regards the availability and scope of the experimental use and ‘Bolar-type’ exemptions. Typically this involves consideration of whether the relevant Bolar provision extends to non generic trials and, if not, whether the study in question is truly experimental and whether it relates to the subject matter of the invention (which is a particular concern when using a patented process or as a research tool). Even within Europe there is scope for companies to be caught out, as the relevant directive has been interpreted very differently across different Member States and in some a great deal of uncertainty remains.

Arraite: In Spain, company liability for drug development risks is heavily regulated and based on an objective approach. There is a legal presumption that, unless otherwise proven, any impairment to the health of an individual who participates in a clinical trial, or which he/she suffers during the year following the trial, is attributable to the investigational medicinal product and thus the sponsor is liable. However, the company would not be held liable if the health impairment is attributable to a patient’s pre-existing condition, or the inefficacy or adverse effects of other medication; but the burden of proof lies with the company.

Samora: Pharmaceutical industry is faced with complex risks inherent in the production of highly sophisticated products. In Europe, the touchstone for product liability is whether the product is defective in itself. Taking also into account the different business models employed by companies in the industry (diversified product model, specialty products, etc) it is logical that tailored insurance coverage programs are needed to address the interests of each company effectively: such insurance should be based on the assumption that given the present state of human knowledge, pharmaceuticals are such products that are inherently incapable of being made entirely safe but whose marketing can be justified despite their known or not-known risks.

8. While no one intentionally sets out to manufacture a hazardous or defective product, even the largest and most sophisticated manufacturers sometimes fall foul of this. How would you set about handling a product recall for your clients? What is the best way to handle PR in this situation?

Ramsay: The first action is to determine if there is a reasonable belief that the product is defective. If the initial legal and technical risk assessment indicates this is the case, then all potentially affected stock should be isolated throughout the distribution chain. It is then imperative that the risk assessment is stress tested and all available information is gathered so as to determine and justify next steps. Not only will due consideration need to be given to regulatory compliance and European and Domestic jurisdictional notification issues also to the handling of your supply chain, traceability of potentially defective product and commercial claims.

Watts: It is a team effort! You need adequate technical resources to assess risk levels and to develop the appropriate response (warning, withdrawal, recall). You also need sufficient legal resources to manage the regulatory notifications, and potential patient and contractual claims (typically on an international network basis). Additionally, PR resources need to be in place early on to manage the media response. Finally, it almost goes without saying that management resources must be available to make all of the above happen. In terms of PR, the crucial thing is to stick to the facts, avoid speculation and maintain credibility. Loss of credibility in the PR response can take a recall to a new level in terms of impact on the business.

Arraite: Development risks represent one of the major changes for pharmaceutical and biotechnology companies. The EU Product Liability Directive introduces “the development risks defence”, and “state of the art defence”, meaning that producers will not be liable for damages caused by defective products if they prove that the state of scientific and technical knowledge at the time the product was put into circulation did not permit the existence of the defect to be discovered. However, Member States may provide exceptions to this defence, and indeed many Member States (including Spain) have derogated it in relation to damages caused by pharmaceuticals. Exposure is, indeed, important.

On the other hand, product recall decisions are on many occasions based on the precautionary principle. The mere suspicion of a risk is sufficient to trigger a recall. We have seen many times that claimants may make reference to a recall in order to try to prove that there is a causal link between the product and the alleged damage (even if the risk that triggered the recall was not finally proven). In other words, claimants may refer to a recall in order to support their allegation of an alleged defect and to try and shift the burden of proving that defect. For this reason, it is important to, at all times, convey a clear message as to what exact reasons led to the recall decision, and whether they are based on a suspected or a proven risk, in order not to hinder the company’s defence in any possible liability suits.

9. Is biotech M&A the only way forward for Pharma?

Ferreiras: Biotec M&A is in general a good way forward for Pharma, as finding dynamic start-up companies could be an interesting strategic action to achieve diversity and to strengthen product portfolio. However, it should not be seen as the only way forward and definitely in no way separately from other structural measures, such as:

(i) Standardisation of processes; 
(ii) Rationalisation of structures; 
(iii) Reduction of costs; 
(iv) Improvement of quality and productivity; 
(v) Expand of shared services; 

Hale: There will continue to be an increase in M&A activity in the sector in 2013. Large pharma has pulled back on expensive R&D for years now and the result is fewer drug candidates in their pipelines. These large companies will continue to look for small to mid-size biotech companies to provide new drugs to produce revenue in the future. Reduced R&D budgets and pipelines as well as expiring patents will work in favour of more M&A activity in 2013.

Watts: Not at all. Depending on what news feed you read pharma acquisitions are either on the rise or in steep decline, but whatever the spin, I can’t see M&A disappearing from the pharma sector. Nor is it the only way forward. Pharma’s natural creativity extends to creative models for growth – for example, finding new ways to grow existing lines in emerging markets and unleash new sources of revenue. There’s increasing emphasis on R&D collaborations, like BMS’s and AstraZeneca’s partnership for certain diabetes products. There’s increased legal encouragement for exploiting new indications for existing active ingredients – reflected in comments in the UK Court of Appeal in 2011 about ensuring the patent system is “fit for purpose”.

Lipkus: I think biotech M&A is a smart play for large companies looking to revitalise their pipelines and for small companies with a narrow but strategic drug development focus. However, there is a need to identify whether acquisitions of biotech companies is likely to lead to the integration of clinical drugs, with a view to increasing chances of success in development and expanding market access upon approval. These companies can afford to grow organically and may benefit from avoiding the disruption that takes place when companies are integrated. (Imagine if Apple were a drug company. M&A would not be the key to moving forward.) When we are talking about Big Pharma in 10 years, I suspect we will be talking about a different set of companies than we were 10 years ago, and not because of M&A.

Knowles: No. M&A activity will undoubtedly continue to feature in the industry. However, the relative size of such deals is likely to be smaller than it has been in the past. There is little evidence that so-called “mega-mergers” have produced an increase in productivity or innovation in Big Pharma. On the contrary, there has been an increase in pharma companies undertaking targeted “bolt-on” acquisitions which bring access to specific assets/technology platforms.

There is also evidence of pharma companies adopting new business models. For example the spin-out of AbbVie from Abbott, and partnering between Big Pharma companies in certain disease sectors such as the AZ/BMS collaboration in the diabetes space.

Kashyap: No at all. M&A activity will undoubtedly continue to feature in the industry. However, the relative size of such deals is likely to be smaller than it has been in the past. There is little evidence that so-called “mega-mergers” have produced an increase in productivity or innovation in Big Pharma. On the contrary, there has been an increase in pharma companies undertaking targeted “bolt-on” acquisitions which bring access to specific assets/technology platforms.

As a result, M&A with biotech companies of various sizes appears to be one of the few avenues forward with a likelihood of sustained success. Reduced R&D budgets and pipelines as well as expiring patents have often proven to be not as profitable as hoped and increased debt associated from these actions is placing further pressure on these companies.

CoE: A patent cliff crisis has arisen in recent years and will continue as top blockbuster drugs continue to come off patent protection and revenues sharply decline from competition from generics. Temporary solutions have included purchasing companies to help build revenue, support stock prices with share buybacks, bolstered dividends, and developing emerging markets. However, the emerging markets have often proven to be not as profitable as hoped and increased debt associated from these actions is placing further pressure on these companies.

As a result, M&A with biotech companies of various sizes appears to be one of the few avenues forward with a likelihood of sustained success. Reduced R&D budgets and pipelines as well as expiring patents have often proven to be not as profitable as hoped and increased debt associated from these actions is placing further pressure on these companies.
10. Can you outline the advantages and disadvantages in a partnered external development (PED) model? How do small and virtual bio-tech firms act as pipeline feeders for major pharmaceutical companies?

Ferreira: Small and virtual biotech firms are definitely playing now an important role towards innovation.

These firms are usually composed by very talented scientists and researcher, often with strong links with universities. Their capacity to turn "less into more", with small but dynamic and efficient teams is a key factor that brings an added value to this market and revealed to be an important business tool for the major pharmaceutical companies.

The development of a new product, as from the identification of the agent causing the illness until the manufacturability of a product, often takes more than 10 years and implies hundreds of millions of Euros of direct costs, being this the reason why the participation of different players in the development chain brings added value in each stage to the those that are participating in the process.

However, one of the key problems of this small and virtual biotech firms is the capacity to find investment sources, which sometimes limit their capacity to continue the research, as well as to ensure the efficiency of their patent organisation and protection.

Ramsay: For large pharma R&D alliances are a form of spread betting. Through partnering large pharma gains access to innovative science and scientists and can research a multiple technologies/targets often at a lower overhead than its own in-house R&D. There is potential to increase the ROI, particularly if investment takes the form of funding for research programmes and also equity in the biotech partner. Participating in a set of strategically strengthened product portfolio in core therapy areas and reduce R&D timescale. In addition, large pharma can leverage its own resources and best practice at the clinical stage. Disadvantages for large pharma are linked to relative lack of control vis-à-vis in-house research methodologies and financial impacts on terminating programmes.

Hale: Strategic alliances continue to grow in the pharmaceutical, biotech and medical device industries, providing much needed drugs to fill the diminishing pipeline of large pharma. Large pharma has pulled back on expensive R&D for years now and the result is fewer drug candidates in their pipelines. Therefore companies also undergoing significant restructuring internally, and shifting to new models of R&D. This, is, in part, to share the cost and risk in R&D as well as produce productivity and access to future products and technology. This shift has resulted in collaborations and alliances between even the big biopharma companies and on a global basis, particularly in the emerging markets.

Lipkus: The external development model is a fantastic idea, in principle. The key advantage for large companies is that they can leverage their innovation dollars a lot further and make a lot more bets on new drugs. The upside for the feeders is that they now have a clear strategy to turn around and implement – and that is what VCs like to see. Conceptually, this model makes sense – both partners are strategically committed to a core task. Of course, much can go wrong. First, large companies are in pitched battle for new drug candidates. When a small, unclaimed company has a molecule worth bringing to the clinic, how much market power will the large companies really have? Also, it is a lot harder for large companies to satisfy themselves as to the promise of a drug candidate when they have not been responsible for the pre-clinical work. So, in that sense, they take on more risk with candidates developed on the outside.

Kashyap: The PED provides benefits like outsourcing or cross licensing non-core technologies, lowering manufacturing costs, outsourcing clinical studies, exposure to newer markets and adding newer drug portfolios. The risks with PED include confidential data leakage, low quality control, cultural differences leading to less control on professional practices, problems arising due to layoffs and retention of manpower due to ample opportunities in related companies.

The small and virtual biotech firms offer efficient and cost-effective means for developing drugs especially in the initial stages of drug development which require in identifying the APIs and subsequent studies on the animals.

11. What is the process of choosing appropriate partners? Discuss what makes small/virtual biotech companies attractive partners?

Ferreira: An attractive small/virtual biotech company is likely the one able to combine a strong scientific background with the capacity of having good investment resources.

A company with such characteristics will likely be capable to get more results and therefore to turn the partnership more proactive and successful.

Moreover, the analysis of the respective patent archives notably regarding the molecules and components developed by a small/virtual biotech company would allow a better understanding not only of the immediate benefits that a partnership may bring to a pharmaceutical company, but also the potential future results of such partnership in view of the innovation abilities shown by the small/virtual biotech company.

Watts: From a business perspective, attractive partners must have interesting product portfolios and sensible development plans, support by robust studies. They must also know how to be good partners in the general sense, i.e. collaborative, honest about their strengths and weaknesses, and good communicators. In terms of choosing appropriate partners, from a lawyer's perspective, this means testing all the standard due diligence issues. Have they protected their products with patent portfolios in key markets, and have studies been conducted in compliance with regulatory requirements? What third party encumbrances exist over the use of their IP, and what litigation or arbitration has occurred, or is likely to occur, in relation to their IP or products? It also means helping businesses understand and deal with the risk identified in due diligence, and, on the occasions when they arise, recognising and acting on red flag issues.

Parker: Virtual biotechs typically have a streamlined infrastructure and highly focused R&D programme. Provided that the match is right, they often represent an attractive acquisition target, whether as a means of filling a gap or expanding the pipeline with a complementary product/technology.

Virtual biotechs are highly focused on one or a small number of product candidates or technologies, and are conscious to ensure that their (typically limited) financing is invested as efficiently and effectively as possible. These characteristics can provide pharmaceutical companies with a more direct and focused insight into the biotech's technology and value, and greater transparency as to the strength of the company's IP portfolio and freedom to operate position (particularly if the documents relevant to their IP position are packaged up in such a way to facilitate the due diligence process). The company's know-how is usually concentrated in a small number of individuals. While this may be attractive from a headcount and integration perspective, the risk associated with the retention of key individuals is greater.

12. By 2015, branded and unbranded generics are expected to be growing faster than patent protected and non-protected branded drugs in Latin America. How can you ensure a patented product is safeguarded?

Samara: Strong patent protection is essential for pharmaceutical companies in order to recover investments made in new products. Parallel to the main patent protection a company may employ other means to secure its exclusivity period, as for secondary patents and patent term extension or a supplementary protection certificate, where applicable. Other ways to extend competition advantage include data exclusivity protection, orphan drug protection and pediatric exclusivity, depending on the product itself. Also, it is important for a company to actively build upon a patent prosecution strategy around categories of products that bear similar characteristics (product markets, market size etc) while carefully following up on competition and regulatory changes in national markets.

Watts: Having patent protection is only one piece of the puzzle. To succeed in Latin America, you need to thoroughly understand the regulatory process in each country of interest. Hopefully, patent protection under international treaties (e.g. NAFTA and TRIPS) and bilateral free trade agreements are going to continue the growth to road of market penetration for branded products in Latin America. Patent holders need to be willing to assert their IP rights where appropriate – it is not enough to simply obtain patent protection without being willing to enforce those rights against infringers. The patent litigation systems of Latin America need to mature but that will only come through use and experience. In Canada Government pricing policies need to be thoroughly understood. For each of these issues, having access to local expertise is essential.

Knowles: For many emerging markets access to basic drugs will be a driving factor in expanding healthcare provision. Initial growth in these markets will inevitably be driven by generic drugs. It is possible for Big Pharma to compete in this arena and a number of companies have generic/branded generic affiliates, such as Sandoz in the Novartis group. However, the branded/generic market is very different to that of innovative drugs and for companies to be successful they will need to operate efficiently and on a large scale in view of the lower returns available.

Longer term, as economies grow, there will be a higher demand for innovative products. However, patent protection and enforcement for pharmaceuticals in Latin America is currently poor compared to established markets. There is a tendency for politicians and governments to undermine independent innovation e.g. by reducing public spending and increasing the number of intellectual treaties or by higher levels of corruption. However, the trend in Latin America is toward greater openness to innovation and the lowering of barriers to new international agreements. This the direction of travel for Latin America and in general for countries aspiring to become more developed economies they will also need to develop domestic innovation, which will need good IP protection to survive. Pharma companies and representatives from developed economies need to continue lobbying for fair implementation of IP rights. Pharma also need to be creative in finding ways of working with emerging markets governments for fair access to medicines, for example by providing compassionate use/discounted access etc.

Parker: The stronger a patent is the more likely it is that the generics will respect it. Accordingly, in most markets it remains rare for even the most aggressive generics companies to launch during the term of the compound patent for the API (save sometimes for a launch shortly before patent expiry where this may be used to obtain a first generic to market advantage). This makes the development phase of new patents (e.g. combinations, formulations, enantiomers, uses, dosages etc) the most commercially important in the portfolio and they should be treated as such in terms of the allocation of resources.

Unfortunately there is no way of ensuring that a patent will be respected or successfully enforced against an infringer, but the following preparatory steps should help the cause: (i) early warning – e.g. intelligence from the regulatory process or from the sales force or other sources that generic launch is imminent; (ii) engaging in pre-action correspondence that sends the right messages and is in line with the overall strategy e.g. if one wants to use the correspondence to trigger events on the merits – should be coordinated for consistency between jurisdictions and to save cost; (iii) conducting a realistic assessment of the merits of the case at an early stage – for business planning purposes and to set the strategy; and (iv) considering the strategy on a
over the competitors in the market. Long term exclusivity and potential market share are considered and whether the patent portfolio can provide sufficient breadth of protection.

Building of the patent portfolio should be a continually managed and periodically reviewed process within a company involving: the management team, technical experts and inventors, and marketing experts who can evaluate commercial potential, in collaboration with experienced patent attorneys. Promising new inventions with commercial potential can be then identified quickly, supporting experiments designed and pursued, and good quality patents obtained.

14. How open is the pathway on biosimilars?

Bell: The pathway towards biosimilars remains unclear. Europe has legislation in place, but there is still much debate about what the US legislation will look like and when it will emerge. Compounding the issue is the broad base of somewhat disparate indications for many biosimilars. A major driver for the future is likely to be the potential for a level of inter-changeability that supports something like generic substitution for biosimilars as opposed to something more like "me-too" branded product competition. Whether biosimilars evolve as generics or "me-too" brands will have a significant impact on strategy and profitability of the biosimilars opportunity.

Feiterra: EU was the first region in the world to have set up a legal framework and a regulatory pathway for "similar biological medicinal products" – more commonly called "biosimilars" – which then inspired many countries around the world.

The concept of a "similar biological medicinal product" was adopted in EU pharmaceutical legislation in 2004 and came into effect in 2005. The first biosimilar medicine was approved by the European Commission in 2006.

Although the process behind the acceptance of biosimilars is yet complex – notably in view of the comparability requirements – EU is developing specific scientific guidelines on biosimilar medicines aiming to provide a strong regulatory process for the granting of marketing authorizations for biosimilar medicinal products.

These guidelines are revised on a regular basis to reflect the experience gained with biosimilar applications and approvals, and try to take into account science and technology improvements, being therefore more and more a relevant pathway to consider.

Haile: Innovative companies have long faced competition from generics companies in the small-molecule field seeking to supply patents and this is only expected to increase with the increased number of innovator biopharma companies who transitioned in recent years from producing small molecule drug (non-biologics) products to incorporating biological products into their pipelines. This has led to the development of biosimilars, follow-on versions of the original biologic medicines (e.g., antibodies) that are independently developed and are intended to have the same mechanism of action as the original innovator's product. Many branded biopharma companies are developing biosimilars, since successful production of a follow-on biologic requires expertise and capital, putting it out of the reach of companies without R&D expertise for large molecules and significant budgets.

In the biosimilars/biologics field, there is no longer a simple alignment of innovator companies against generics companies. As biosimilars are approved in the US, much of the biologics/biosimilars litigation will be between large branded companies.

Lipkus: The jury is still out on this one. Although regulators have approved some biosimilars – e.g. erythropoietin, filgrastim and human growth hormone – the big test will be for monoclonal antibodies in the rheumatologic and cancer spaces. One company out of Korea, Celltrion, has filed applications in most developed countries. They have received approval in Korea, but the big test will be Europe. If Europe approves their first product – infliximab - then that will instantly validate the biosimilars space. However, if the EMA and others shy away from approval, then it could be a long road for biosimilars. The pathway in the US also faces its own unique problem – their regulatory pathway contains a Byzantine patent pathway that no company would dare test. Until the pathway is refined, I think we can expect companies to file regular biologics submissions and argue for lightened clinical testing.

Kashyap: The biosimilars pathway can be looked from three perspectives, (a) innovator and generic companies’ perspective; (b) need for cheaper medicines, (c) government and regulatory perspective. Increase in world population puts pressure for need of medicines and this pressure is felt more acutely in developing country sector. Although biosimilars solve the problem of cheaper medicines, but it also increases the pressure on the regulatory bodies not only to ensure high drug safety standards for biosimilars but maybe raising bar for their safety standards. While the innovators see them as threat to their investments, revenues and development of new innovator drugs, the generics consider them in respect of increasing their market share and revenues.

Parkett: The European Medicines Agency (EMA) has authorised 14 biosimilars (although 2 have been withdrawn) and recently undertook an initiative to update the regulation of biosimilars via a series of revised and supplemental guidelines, including new product specific guidelines – biological drug product (BPD) guidelines. These guidelines are an attempt to harmonise regulatory requirements for biosimilars, biologics and monoclonal antibodies. However, the regulatory requirements may vary in this area and more countries may follow, including plans afoot at the FDA. Although it remains to be seen when the first biosimilar monoclonal antibodies will be approved under the EMA’s scrutiny, the South Korean manufacturer Celltrion announced last year that the Korean Food and Drug Administration approved the world’s first biosimilar monoclonal antibody medicine, Remsima (infliximab), and European applications are pending.

global basis e.g. what are the prospects for obtaining a quick and favourable outcome in a ‘patient-friendly’ jurisdiction and then ‘exporting’ that decision to try to influence the position in other markets?

Cox: Court records in key commercial markets around the world show that patents protecting blockbuster drugs are constantly being challenged. It is imperative that originator companies use the services of patent attorneys with considerable expertise in pharmaceutical patent litigation. This is because if a new compound leads to a blockbuster drug, then the patents protecting the drug are almost guaranteed to be scrutinised by teams of lawyers in key commercial markets with an aim to invalidate them.

Having the patent specification drafted or at least amended during the application stage to meet the requirements of the local patent laws is another imperative. Subtle differences in patent laws between countries may lead to weaknesses in patents in key commercial markets and local attorneys experienced in pharmaceutical patent litigation can assist during drafting and/or prosecution to prevent competitors exploiting such weaknesses.

13. How can companies build and monetise a patent portfolio to replicate the success of intellectual property in the technologies sector?

Haile: It is critical for life sciences companies to build a strategic patent portfolio that both protects its products and will withstand challenge from competitors. Companies should build the portfolio by updating inventive aspects as drugs go through development and into the clinic, beyond the initial discovery of a drug or product, such as patenting new formulations and delivery methods (e.g., injectables to orals), specific therapeutic regimens and alternative indications. In an industry where products can often take 8-10 years before they come onto the market, IP assets are often the most significant assets a company has for many years.

Watts: Firstly, one should only query whether the sector, as a sector, has really been successful. There are shining beacons of success but also numerous high profile insolvencies with major brands, whose portfolios are only monetised as a result of the insolvency. For pharma companies, the ability to monetise patent portfolios has been based on the more traditional, but very successful, model of selling patented products. It would be a mistake to jump to the conclusion that pharma should be seeking to replicate the portfolio sales and licensing that has been taking place in tech. The correct approach is holistic, looking at how the interaction of patents, regulatory and government pricing/reimbursement best works for the particular pharma business. There is no one-size-fits-all solution here.

Parker: The principal routes for generating revenue (directly) from a patent portfolio include selling, licensing and raising funds from financial institutions using patent assets. In the technologies sector this has produced massive revenues, including for so-called ‘non-practicing entities’. Whilst the technology sector is to some extent more amenable to this business model as a consequence of the sheer number of players, there may be scope for pharmaceutical companies to do more to capitalise on their patent assets. By generating or acquiring patents with licensing as well as protection in mind and addressing this when conducting patent audits, pharma companies should be able to exploit their portfolios to generate royalties (and such portfolios may also have defensive value in terms of freedom to operate). Licensing an entire patent portfolio as a source of revenue rather than as a means of maintaining the monopoly around key assets is a change in approach that will not suit every company. That said, although there are a few examples of companies that derive the bulk of their revenues from royalty payments (e.g. FDL Biopharma and its phage display patents), there is no need for the decision to be a binary one and no reason why ‘traditional’ R&D-focused companies should not also more to generate royalty streams.

Cox: From the point of view of the start-up biotech company, building a strong patent portfolio is an important way to increase its strategic business value. Such companies often arise on the back of a single invention that is their key asset. Patents drive investment from venture capital, initial public offerings and other sources, as well as mergers and acquisitions by big biotech and pharma. To obtain this investment, the investors or companies must be persuaded that the patents protecting the start-up’s invention(s) will secure an advantage
but also for new drugs for the diseases where limited or no drugs are available. In future the big pharma companies will need to invest heavily in R&D to keep their drug pipeline evergreen not only for existing diseases rapidly capturing branded drug market. strong leadership to quickly evolve and embrace change if they are to continue to survive. ing a larger number of new drugs with possibly smaller peak year sales, which reduces the risk of the business being reliant upon one placement products. Some companies such as AZ and Pfizer have had acute exposures to patent cliffs, which has resulted in drastic cuts to price their drugs for maximal therapeutic and commercial short-term impact. The patent cliff has exposed a fundamental weakness in the Big Pharma business model, namely, the reliance upon a few “block-busters” to price their drugs for maximal therapeutic and commercial short-term impact. The “patent cliff” may be a phenomenon for a product and even for a company with a cluster of products expected to experience generic competition at the same time, but it is not like there have been any real surprises. Ever since the advent of generic competition, the industry has had to address the significant dislocation that comes with the rapid decline in sales of a major product. In general, the industry has coped reasonably well. Companies have portfolios of products and financial strategies to keep revenues flowing, and sales and marketing investments accordingly. With respect to employment upheavals, mobility within large pharmaceutical companies and across the industry generally supports the continued maintenance and growth of a qualified talent pool.

Ramsay: ‘Patent cliffs’ have a significant impact on the pharma industry but this stems from a confluence of factors. It is the patent cliff in tandem with weaker pipelines, increased cost/ timeframes to get products to market, early entry of generics, greater regulatory responsibilities and the growing need to demonstrate that new or second generation products have significant incremental benefits. All of these factors have led to market consolidation, therapeutic specialisation, global cost reduction programmes and sharing of R&D risk-sharing through partnering and outsourcing. Many businesses have been learned and a more robust and leaner industry, with some new players emerging, is the consequence.

Watts: There is increasing recognition among industry leaders and regulators that the industry will need to diversify away from blockbust er drugs towards more drugs for smaller markets to address unmet needs. Personalised medicine is the logical end-point of that process. Leadership will become much more important in this regard, and nothing should be out of bounds for questioning – not programs, policies, people, cost or structure.

Lipkus: The ‘patent cliff’ has ‘produced winners and losers. The big winners of the 1990s are poised to become the losers of the 2010s where they have failed to capitalise on their assets. Their pipelines and AstraZeneca produced the top-selling drugs in the world at their peaks (Lipitor and Symbicort respectively) and empirical-sophisticated biochemistry with unparalleled marketing. However, the world has changed and produced a new wave of winners – think Amgen, Abbvie and Roche, who have developed blockbuster biologics capabilities. These companies have exploited regulatory barriers rather than patent barriers to get to the top. In my view, the next phase of winners – led by Gilead and Vertex – will re-exploit patents with unique molecular-targeting strategies that increase pipeline velocity and find creative ways to price their drugs for maximal therapeutic and commercial short-term impact.

Knowles: The patent cliff has exposed a fundamental weakness in the Big Pharma business model, namely, the reliance upon a few “block-busters” to drive growth. As regulatory and health economic hurdles have increased, it has proven more difficult to find new re- placement products. Some companies such as AZ and Pfizer have had acute exposures to patent cliffs, which has resulted in drastic cuts and downsizing. Novartis appear to have successfully moved away from the block-buster model and have instead focussed upon providing a larger number of new drugs with possibly smaller peak year sales, which reduces the risk of the business being reliant upon one or two key products for survival. Novartis and some of the other Big Pharma companies have diversified their generic businesses including generics, OTC and consumer healthcare to spread the risk. All of the Big Pharma companies have known for a long time that their patent cliff has been approaching and yet many appear to have reacted too slowly to avoid it. Pharma companies will need strong leadership to quickly evolve and embrace change if they are to continue to survive.

Kashyap: Patent Cliff creates a wide spread impact by shifting the pharma industry into two clusters, one of big pharma and other of generic companies. The big pharma companies see it as unprecedented decline in their revenues and in process may try to implement alternate strategies like litigation, cross-licensing, off-shoring or outsourcing of manufacturing to stop or delay market capture of branded drug by generic drugs. Alternatively, the generic companies create a path of price competition by providing for cheaper generic drugs by rapidly capturing branded drug market.

In future the big pharma companies will need to invest heavily in R&D to keep their drug pipeline evergreen not only for existing diseases but also for new drugs for the diseases where limited or no drugs are available.

Parker: The ‘patent cliff’ has been attributed with prompting the trend towards diversification, focus on emerging markets and expanding the pipeline of new medicines. From a patent lifecycle management perspective, one of recent years supports the trend towards biologics, which typically remain less vulnerable to patent expiries as a result of the higher barriers to entry and tougher regulatory regimes for biosimilars (e.g. if one compares therapeutic monoclonal antibodies with ‘traditional’ small molecule generics).

In terms of patenting and litigation strategies, the fears that the European Commission’s Sector Inquiry would give the generics the upper hand in future patent expiry battles appear not to have been borne out. It should be noted, however, that when the new European unified patent court (the “UPC”) goes live in future (most likely in 2015) the impact of patent expiries may become even more dramatic, as for the first time it will be possible to revoke patents on a Europe-wide basis. However, it is thought likely that pharmaceutical companies will opt their most valuable patent assets (at least) out of the new system during the transitional period of seven years.

Cox: The sharp decline in revenues upon expiry of patents protecting blockbuster drugs is a stark reminder of the precariousness of the pharmaceutical industry and the rise and fall of the fortunes of big pharma. The magnitude of the revenue streams means competitors and even government agencies continue to take action in key blockbuster markets to expedite patent cliffs. One lesson we have seen companies learn either through success or failure is that patents for new potential drugs and biologics should always be drafted by patent attorneys with considerable experience in pharmaceutical patent litigation. Secondly, that the patents should be drafted at least by someone experienced and local to the market with local knowledge and development, and sales and marketing investments accordingly. With respect to employment upheavals, mobility within large pharmaceutical companies and across the industry generally supports the continued maintenance and growth of a qualified talent pool.

16. What regulations, charges or other restrictions should an organisation consider before entering your jurisdiction?

Samara: Due to the austerity measures taken to combat the extreme financial crisis, the Greek legislature has been very active amending pharmaceutical regulation to control public expenditure for health care. Law 4052/2012, as amended, introduced a number of changes in the market including promotion of generics via compulsory prescription by active substance, e-prescription for almost all medicines; a cash back and a rebate mechanism with retrospective effect; consecutive reductions in the maximum prices for both original and generic pharmaceuticals; reductions in profit margins for pharmacists; e-procurement for the supply of medicines to public hospitals; a one-off special payment by MAHs for the inclusion of prescription medicines in the positive list. All these measures, coupled with the considerable ‘haircut’ of the state bonds the pharmaceutical companies had acquired in settlement of overdue hospital debts should be weighted accordingly by organisations.

Haile: The regulatory/compliance burden on Life Sciences companies, already huge, shows no signs of decreasing. Big biopharma have “deep pockets” making them attractive to anti-bribery and anti-corruption (ABAC) investigations and enforcement, with large fines being imposed where failures are uncovered. Last year in the US alone, GSK announced a $3 billion settlement; Abbott agreed to pay $1.5 billion; and Johnson & Johnson agreed to pay $2.2 billion to settle charges of off label promotion. There is also increased enforcement activities in the UK, China, and Russia, and increased global coordination among law enforcement agencies and regulators. Whether going into the US, Europe, China or other markets, companies must understand and implement strict compliance programs.

Watts: The UK is a great jurisdiction for pharma companies to invest in. Firstly, there is already large scale private and public funding for basic science. We also have a sophisticated regulatory regime, and benefit from wide ranging international treaties and trade agreements. Contrary to its historic reputation, the UK courts in fact uphold most pharmaceutical patents. The UK has recently become even more attractive for pharma with the advent of the Patent Box – legislation that allows corporations to apply for a lower rate of corporation tax for profits earned after 1 April 2013 from UK or European patents. Finally, very recently the UK government has announced a proposed change to the Patents Act which will allow more R&D activities for clinical and field trials to be conducted by companies without risk of patent infringement claims.

Arrieta: As mentioned before, pharmaceutical companies operate in a highly regulated environment, which affects almost every single aspect of their activity. It would be impossible to summarise this in just a few words. However, this is not Spain specific, and pharma companies present in other western markets will not be surprised by this. Nevertheless, there are other important aspects that must always be put to one side when assessing any strategic decision concerning the Spanish marketplace. Firstly, the regulatory environment has been, and is being subjected to continuous and sudden changes. The regulatory authority responsible for regulating biologicals, medicines and medical devices in Australia is the Therapeutic Goods Administration (TGA) before it can be imported, exported or supplied for use in Australia. Medicines and biologicals for experimental use in clinical trials may be exempt from having to be included on the ATRG.
Australia has a two-tiered system for the regulation of medicines, including complementary medicines where:

- Higher risk medicines must be registered on the ARTG, and
- Lower risk medicines containing pre-approved, low-risk ingredients can be listed on the ARTG.

A ‘sponsor’ is responsible for applying to have a therapeutic good included on the ARTG. A sponsor must be an Australian resident, or an incorporated body conducting business in Australia with a local representative.

Advertisements for therapeutic goods can be presented in several forms in Australia, including: magazines, newspapers, television, radio, internet, posters, billboards, and medical journals. However, advertising prescription-only and certain pharmacist-only medicines to the general public is prohibited.

Patents
Pharmaceutical and biotech companies are proficient in obtaining Australian patent protection for their new products and processes. However, it is equally as important to identify patents which may be infringed if a therapeutic product is imported or manufactured in Australia. A patent search and a freedom to operate opinion prepared by an Australian patent attorney will assist in identifying potentially relevant patents.

Validity opinions may then be prepared and licensing deals sought in a strategy to enter the Australian market with ‘eyes wide open’.

Australia patent law has provisions for an extension of term of up to an additional five years for a patent claiming a pharmaceutical substance to offset time waiting for regulatory approval from the TGA and having the product registered on the ARTG. During the term of extension, however, the patent owner’s rights are limited to therapeutic use of the patented pharmaceuticals in humans.

Trade Marks
It is important to select trade marks for therapeutic goods that are not likely to cause deception or confusion and this has been illustrated through a number of court decisions in Australia. An Australian trade mark for a therapeutic should avoid:

- infringement of any pre-existing registered trade marks, or
- contravention of the Trade Practices Act 1974 (Cth) for misleading or deceptive conduct, or representation; or
- claims under the common law of passing off.

As part of the process for registering or listing therapeutic goods on the ARTG, the TGA will closely examine the trade/brand name of the therapeutic goods in order to ensure that the name, once registered or listed, will not mislead or confuse the public.

17. Is regulatory harmonisation a realistic possibility or nothing more than a pipeline dream?

Samara: While all pharmaceutical regulatory organisations make every effort to ensure public health through access to safe and effective medicines, yet, global regulatory approvals suffer from delays, complexities along with added costs. This goes along all stages of pharmaceutical development with global recession, high R&D cost, high manufacturing costs, competition from biosimilars, generic industry and drying drug pipelines, the emerging markets offer excellent opportunities for them to invest, collaborate and utilise the low cost and easily accessible resources such as cost effective professional and experienced manpower, CRAMS/CRMS, Clinical research facilities, outsourcing R&D facilities and other pharmacists and biotech related business services (such as third party handling of business analysis, regulatory affairs, financial management, etc.).

Knowles: China is encouraging the growth of innovative industries in China. This provides an opportunity for the pharmaceutical industry to invest in China and benefit from the domestic growth and access the scientific talent which will inevitably emerge. However, there are also some worrying trends in China, particularly around the enforcement of IP rights covering pharmaceuticals. It remains unclear how the Chinese courts and government will handle IP litigation. If innovative pharmaceutical companies cannot reliably enforce its IP rights this could stall investment in China. For example if China adopts some of the IP practices seen in India, this would seriously deter pharmaceutical investment in China.

Other growth areas include Turkey, which has shown strong growth as it moves to possible membership of the EU. However the economic woes of Europe may have an impact on this growth as pressure on healthcare budgets grow.

Ramsay: At the level of the European Commission we are seeing increased harmonisation. The use of EU regulations not directives, such as the proposed clinical trials and medical device regulations, is aimed at delivering greater harmonisation in practice and not just in theory across member states. However, regulatory harmonisation in Europe remains an aspiration rather than a reality.

Liphsan: We have been talking about regulatory harmonisation for years, and there are many cynics. A big test will be the Trans-Atlantic Free Trade Agreement (TATAF), between the US and EU, currently being negotiated. These negotiations may include a form of regulatory harmonisation for drug approval, with a view to decreasing the burden on regulatory agencies to do all the work from scratch. Regulatory agencies have been cooperating more and more, though on an informal basis. In this age of government austerity, there is definitely a greater desire for agencies to leverage each other’s efforts and I do believe we will see more formalised harmonisation going forward.

18. What key trends do you expect to see over the coming year? And in an ideal world what would you like to see implemented or changed?

Bell: Despite economic and political uncertainty, a plethora of new, innovative molecules are expected to come to the market in the next few years, and the mature markets of the US and EU remain critical battle grounds for pharma. The US remains the largest single pharmaceutical market, and it is likely the most attractive market into which to launch innovative new products. While the EU continues to face significant financial pressures, healthcare remains high on the political agenda and the well-established infrastructure will continue to support the life sciences industries. The emerging markets continue to receive attention from pharmaceutical executives, but the opportunity will likely require more country-specific strategies and investments than has been the case in the past.

Ramsay: This is a subjective question and answers will vary from company to company and be dependent on the nature of the product. In a recent survey we asked clients in which countries do they have the greatest need for legal talent? Taking this as a proxy for where the greatest opportunities lie, the top responses were China, Russia, Latin America and India. We also see an increasing focus on Africa.

Haile: Established Life Sciences companies are investing significantly in the BRIC/G20 countries, where population size and increased wealth and economic growth has led to an exponential increase in the manufacture and sale of drugs, therapies, as well as renewed focus on pharmaceutical innovation and competition laws in those countries. The emerging markets are increasingly important as clinical trial sites, and this increases a company’s exposure to government oversight and enforcement (including clinical trial governance, fraud, and ABAC issues). These countries are investing to upgrade their research/clinical development and manufacturing skills and facilities, and can now offer cost effective and high quality alternatives for global biopharma companies. While Indian companies have long provided active pharmaceutical ingredient (API) manufacturing for global pharma, Indian and Chinese biopharma companies are emerging as global biopharma companies in their own right. Additionally, many global biopharma companies are now looking to Asia as a potentially significant market for them, given the population numbers and that patients are under-serviced with prescription medicines. This is in contrast to the US and most of Europe, where patients have a huge amount of choice in this area.

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17. Is regulatory harmonisation a realistic possibility or nothing more than a pipeline dream?

Samara: While all pharmaceutical regulatory organisations make every effort to ensure public health through access to safe and effective medicines, yet, global regulatory approvals suffer from delays, complexities along with added costs. This goes along all stages of pharmaceutical research and development. As pharmaceutical regulations are by nature sovereign laws, it is difficult or even impossible to harmonise (see the European example as an example of difficulty). However, as harmonisation does not necessarily mean homogenisation, adopting a common set of rules that bring together regulatory requirements across the world for medicines, may be an achievable and, certainly, desirable goal for pharmaceutical companies.

Ramsay: At the level of the European Commission we are seeing increased harmonisation. The use of EU regulations not directives, such as the proposed clinical trials and medical device regulations, is aimed at delivering greater harmonisation in practice and not just in theory across member states. However, regulatory harmonisation in Europe remains an aspiration rather than a reality.

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Arrieta: Regulatory harmonisation at an EU level is proving to be a hard process, mainly due to different interests of the States. In any case, harmonisation is, in the best scenario, a very lengthy process. A very recent example is the Patients Information Directive. The first consultations were six years ago and, still, there is no visibility as to when (if at all) the Directive may be approved. Member States, on the other hand, retain their powers regarding reimbursement and price fixing of pharmaceuticals, which results in great differences among the EU territory. In Spain, we must also take into account that cost-cutting measures taken at a regional level differ greatly. On
Ferreira: The coming year will likely bring "more of the same". Austerity will continue to be the key word and therefore Governments will continue to chase less expenditure. Social services, including the National Health Care System, will continue to suffer with severe cuts, which will continue to impact the pharma industry. This landscape will likely have a negative effect in the capacity of the industry to bring innovation, which fact raises concerns as of the ability to continue to provide efficient and innovative health care to the patients.

Ideally, we would like to see the market more focused in innovation and patient care rather than the price pressure, as well as increasing the importance of small biotech companies – notably by turning easier their access to the necessary funds – in the development of new components that can be used then by the pharmaceutical industry.

Samara: In the short term, it is expected that generic manufacturers will try to further utilise on the opportunities presented by the many patent expiries, while pharmaceutical companies will try to accommodate their business models (perhaps through further mergers and acquisitions as well as cost reductions) in order to maintain a competitive edge. At the same time, governments are expected to further increase national price controls and other health care cost- containment measures, which, effectively, lead to concentrations of credit risks for pharmaceutical companies (especially, in countries of southern Europe). In an ideal world, market forces and regulation should be coupled together in order to ensure that safer medicines for all people are put quicker in the global market.

Ramsey: We cannot expect to see any let-up in generic competition, pressure on pricing, increased hurdles on market access or the trend toward greater transparency. The scepticism of consumers and regulators continues; evidenced by the number of pharma inquiries and the introduction of transparency obligations, through new legislation or revised industry codes.

Sophisticated solutions to healthcare problems will also mean we see more complex collaborations and business models within the industry (both existing and new players) as high-tech IT, data and communications solutions become an integral part of product differentiation, drug delivery and real-time patient monitoring.

These changes have a common strand - the patient and the patient's needs are at the centre of these new business models and capabilities.

Haie: Pharmaceutical companies are finally beginning to realise that their "one size fits all" model is no longer the norm. With whole genome sequencing being available at reasonable costs, and a greater understanding of genetic variation and heterogeneity of disease, pharma companies now understand that there is a greater need for individualised therapeutic decisions. However, it is short-sighted to think that the "personalised medicine" approach will result in a reduction in overall revenues for a company. In fact, the ability to predict adverse drug reactions or resistance to a drug, will reduce the cost of going from R&D to the clinic to the market. Diseases will be detected more precisely and the right patients will be entered into the right clinical trials, thus, a reduction in the failure rate of clinical trials.

Watts: As an IP lawyer, one of the key trends I expect to see is a move towards greater patent harmonisation. With the Unified Patent Court soon to become a reality, we can expect finally to have a court with European-wide jurisdiction for patents, and a new unitary patent (with unitary effect across all participating states). Ideally this will make the patent filing process, and the enforcement of patents, more affordable and efficient, and will help minimise forum-shopping. The passage of the America Invents Act in the United States has more precisely and the right patients will be entered into the right clinical trials, thus, a reduction in the failure rate of clinical trials.

Lipkus: I see two trends that we will continue for the next several years: better-targeted drugs and more sophisticated pricing. Better-targeted drugs will be approved faster with less testing. This is the signal that the FDA sent in approving Kalydeco last year based on a very specific mutation in the cystic fibrosis gene. While it means that the drug's patient population will be small to start, the drug sponsor is not prevented from running Phase IV tests that expand the label over time. This approach has the ancillary benefit of justifying a high price at the start, with the price declining as the label expands to cover more indication. On the pricing front, companies will face a harsh reality as targeted drugs come to market - not every drug can bear a price in the tens of thousands of dollars. Companies that find ways to set prices based on the health impact achieved by their drug, as agreed by price-setters, will succeed.

Knowles: Increased pressure on health care budgets, particularly in Western Europe will see profits from this region decline further.

- Further shrinkage of the pharma industry as the impact of patent cliffs work through.
- In an ideal world more generous IP protection of pharmaceuticals is required. In particular:
  - more reliable and longer periods of regulatory data exclusivity e.g. the generous provisions in Europe;
  - introduction of patent term extensions in more countries, particularly Canada and China;
  - better implementation of TRIPS requirements.

Kashyap: The concept of ideal world is unimaginable considering the pace with which the world is changing. However in the real world the key trends in coming year/s may involve a more holistic approach in healthcare systems, wherein the biotech and pharma industry may have to work in close association with governments and regulatory bodies to provide patent centric healthcare services, evolve tailor made pricing strategies for newer and existing markets, adhering to higher ethical standards and evolve tailor made IPAM strategies for adhering to local IP laws. Trends like M&A’s, litigation, outsourcing of CRM’s, cross-licensing and outsourcing and off-shoring of R&D to emerging markets may also be seen.

Parker: A trend that will continue over the coming years is towards increasing transparency within the industry, particularly as regards clinical trial data. That said, there are a number of issues surrounding the commercial sensitivity of patient-level data (in particular) that need to be worked through (and the legal challenges to the EMA's access to documents policy brought by AbbVie and InterMune will provide a focus for this).

On a related point, transparency with regard to relationships with healthcare professionals is also a developing area. Examining the ways in which industry can continue to interact with healthcare professionals while maintaining appropriate ethical standards and preserving their independence are at the forefront of industry and regulatory discussion in both Europe and the US.

Another important development over the next couple of years will be the coming into effect of the Unified Patent Court in Europe and availability for the first time of a unitary European patent. The new system, which is aimed at simplifying the enforcement of patents in Europe, should come into existence by mid-2015, but companies need to start taking action now to get to grips with how the new system will work and deciding whether or not they want to opt any of their patents out of it during the transitional period of seven years (a balancing act that may look different for different parts of the pharmaceutical industry, for different products and different types of patent).

In terms of change I would like to see developing economies adopt a more measured, predictable and fairer approach to patent matters than is evidenced by recent compulsory licensing decisions.

Arrieta: One of the major, and most long-awaited, foreseeable developments in Spain will be the enactment of the new pricing and reimbursement regulations. A draft royal decree is reportedly due to be issued for consultation shortly, and expected to come into force by year end. As yet, little is known as to the approach it will take. Ideally, it should provide for specific and objective decision parameters which facilitate effective judicial control of administrative decisions; enhance coordination between the marketing authorisation process and the pricing reimbursement process to avoid duplication of technical evaluations (and, particularly, their subsequent reiteration at regional level); ensure the participation of all stakeholders in the pricing and reimbursement process (industry, doctors, and patients); and provide mechanisms to enable companies to apply government fixed prices only to medicines actually reimbursed (and not to those sold in private markets).