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Business Development & Licensing Journal

For the Pharmaceutical Licensing Groups

Contingency Planning for a Possible UK EU Breakaway

Pharma and Biotech Valuations: Divergent Perspectives

Continuing Strength of the IPO Market

How Pharma Underestimates Sales of its Top Products

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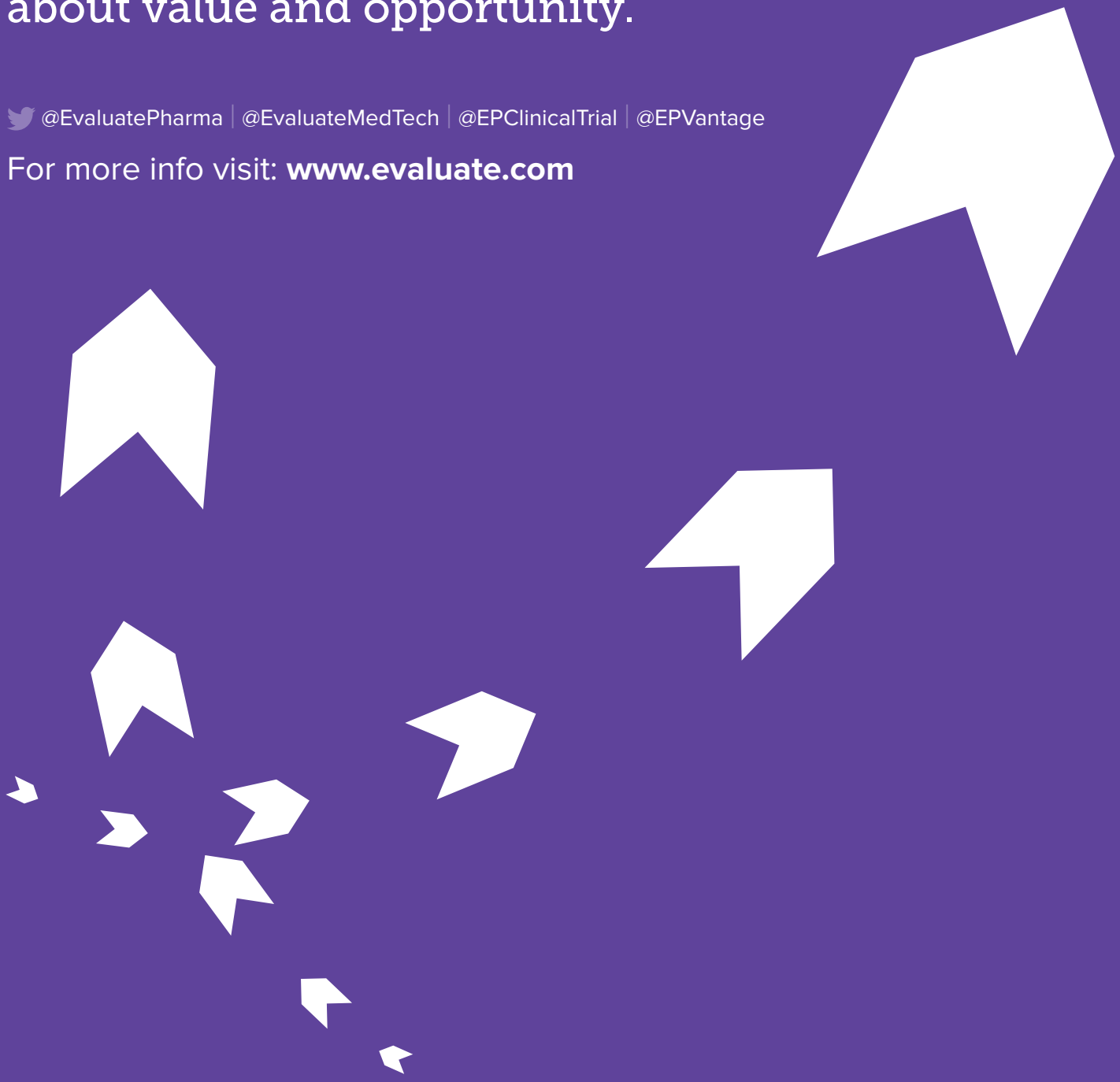

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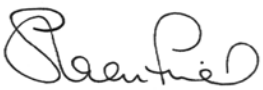
Welcome

Over the next few issues we will be seeing some changes to the PLG's Business Development & Licensing Journal. First started in Spring 2006, next year will see the Journal's Tenth Anniversary. The industry has certainly changed significantly over this period and so not surprisingly we will be making some changes to the Journal.

Many publications have switched from hard copy to being available electronically and due to increasing print cost and higher costs of distribution it is felt that the BDJ should also go this way. On a personal note, I do prefer to have hard copy to read – something non-confidential for those long flights! Also, hard copy does represent a value-add for our PLG members. However, the plan is to keep some hard copy which will still be available at joint meetings and if you have specific views on this topic, do make your thoughts known.

Electronic copy will be available on the main European web site sent via an email link. We will also be making some changes to the content and plan to include some interviews with key BD opinion and thought leaders.

With the recent political changes across Europe it seemed a good time to address the interesting topic of European unity – as in our article on Repositioning of Deals. It is good to see that the various national PLGs are increasingly working together with the PLG planning to have a stand at the forthcoming BIO-Europe event in Munich, so we will be pleased to welcome many of you there. In addition, we are looking forward to an exciting programme for the IPLS meeting in Berlin, but in the meantime I hope that this issue will make for some interesting summer reading.



Sharon Finch
Editor, *Business Development & Licensing Journal*

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Repositioning Deals – Contingency Planning for Possible UK EU Breakaway

Withdrawal from the European Union is possible and the UK Government has committed to holding an in/out vote by the end of 2017 at the latest. With this in mind, now is a good time to assess potential risks in existing and future agreements and future-proof deals against the contingency of a UK exit from the European Union (EU). This would be a novel situation and the consequences of an EU exit would only be known after a lengthy period of renegotiation to determine the UK's future relationship with the EU. The ongoing debate about the UK's future in Europe needs to take due account of the views of the sector and its shared vision of the UK's place in or outside the EU.

By Helen Cline, Legal Director, Life Sciences Group, Pinsent Masons

Since UK Prime Minister David Cameron's Bloomberg speech in January 2013,[1] the Conservative Party has been committed to holding a referendum on the UK's membership of the EU. The Conservative party's victory in the general election, and the recent Queen's Speech, mean that the UK will definitely have an in/out referendum on EU membership before the end of 2017.

Establishment in the EU gives companies access to a single market of some 500 million people, with a combined GDP of £11 trillion, in which companies can freely trade. Consequently, UK is seen by international companies as a bridgehead to the EU market and there is considerable inward investment from both EU and non-EU businesses. There is a real danger that any uncertainty in the run-up to the referendum and during any possible renegotiation of the UK's relationship with the EU could lead to foreign companies diverting or postponing investment into the UK.

Recognising the possible consequences of this uncertainty, Mark Carney, Governor of the Bank of England, has recently called on the government to bring forward the referendum.

In an interview with the BBC in May 2015, Mark Carney, Governor of the Bank of England, said: "I think it is in the interests of everybody that there is clarity about the process and the question and the decision."

In a speech to the House of Commons on the day the EU Referendum Bill was published,[2] Mr Cameron suggested that he wants the Bill to pass through Parliament in "extra quick time" which may be an indication that the referendum on the question, "Should Britain remain a member of the European Union?" could be as early as next year.

Is Withdrawal Possible?

Withdrawal from the EU is possible (see Box 1). However, the UK has been a member of the EU for just over 40 years and divorcing itself from such an intricate and complex relationship could take years, as would determining the boundaries of its future relationship.

Disentangling UK domestic legislation from EU law would be a complex process. It will be important to take time to ensure that the unravelling and retying of the UK's ties with the EU are ultimately successful and beneficial. Would a non-EU UK keep all or some of the rules and procedures of EU legislation? Many believe that existing UK legislation is likely to be unpicked and changed – however this is not necessarily the case. For practical reasons, the UK is likely to keep significant amounts of laws of EU origin as in many areas such as medicines regulation and data protection the trend is towards harmonisation internationally.

This is a novel situation and the full impact of a withdrawal is impossible to

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Box 1: Withdrawal from the EU

The Process "Any Member State may decide to withdraw from the Union in accordance with its own constitutional requirements." Article 50, Treaty on European Union.

A Member State that wishes to leave the EU is required to notify the European Council of its intention to do so. Due to the complexities of leaving the EU any withdrawal is likely to involve lengthy negotiations. To date, no Member State has left the EU or its predecessor bodies. Greenland, an overseas territory of Denmark and not a Member State as such, did leave the EU in 1982.

The Withdrawal Agreement
Depending on the result of negotiations and if the UK were to decide to split from the EU, but still wished to retain the benefit of the Fundamental Freedoms (free movement of persons, goods, services or capital) of the internal market, it would have to choose a model of integration without membership such as that enjoyed by the European Free Trade Association (EFTA) countries. The European Economic Area (EEA) agreement and the Swiss bilateral agreements may serve as blueprints for future negotiations.

Possible Consequences
The Treaties and all existing directly applicable EU law would cease to apply to the UK from the date the withdrawal arrangements entered into force or, failing that, within two years after notification unless the Member State and the UK unanimously agreed to extend this period. A new legal order / regime would need to be agreed. Unless the UK were to negotiate some model of integration without membership, the Fundamental Freedoms would cease to apply.

predict. If the UK were to vote to leave the EU, there would be a period of renegotiation, in which there would be continuing uncertainly until the UK's new status in Europe was agreed. As outlined in Box 2, the UK would have a number of options for renegotiating its relationship with the EU following a no vote in the referendum. The consequences will depend on which path the UK decides to take and, of course, which options the remaining Member States leave open.

Whatever the final outcome, businesses should prepare now for a possible UK exit from the EU, anticipate the risks and begin contingency planning, regardless of whether they believe it will happen or not. Now is, therefore, a good moment to explore the potential implications of a UK exit from the EU and any renegotiation of the UK's relationship with the EU for existing and future partnering deals.

This article considers some areas of possible risk and suggests some ways to mitigate these risks. It also considers some other implications for businesses and goes on to highlight why there is a need for engagement in the ongoing debate.

Contingency Planning for an EU Exit

As a first step it is probably a good time to audit existing partnering arrangements to identify any potential contractual exposure. In addition, where possible, safeguards should be included in future agreements so as to future-proof these against a UK withdrawal from the EU.

Consider whether an EU exit would or should constitute a force majeure event – essentially an unnatural event occurring outside of contracting parties' control – and trigger either party's ability to avoid contractual obligations or liabilities.

Box 2: Alternative Models for Renegotiation

Alternative models for renegotiation open to the UK if the vote is to leave the EU include:

- Negotiate to exit the EU completely
- Retain membership of the European Economic Area (EEA) as a member of the European Free Trade Association (EFTA)
- Return to EFTA and negotiate an arrangement similar to Switzerland's
- Negotiate a bespoke arrangement using these agreements as a blueprint
- Negotiate a series of bilateral trading arrangements within the overall aegis of the World Trade Organisation (WTO)

Contractual implications arising from possible uncertainties around currency should be considered and, although the tax implications are beyond the scope of this article, it is worth mentioning the Interest and Royalties Directive, which enables royalty payments and interest payments to be paid in other Member States free of withholding tax. Leaving the EU would mean that UK companies could no longer rely on this Directive and would instead have to rely on any double taxation treaties the UK enters into with each of the remaining EU Member States. This could mean that companies could have to pay foreign withholding tax on royalty income flowing into the UK.

The territorial scope of existing and future agreements should be reviewed. Existing arrangements may well refer to "the EU" and therefore may need amending to ensure that the contract is effective within the UK following an exit from the EU. In addition, intellectual property licensing arrangements may be tied to a moving definition of "the EU". A UK exit could lead to the licence no longer covering the UK. Consider, therefore, incorporating an obligation in those circumstances to execute any necessary additional licences to avoid infringement of IP rights.

Inserting a generally worded hardship clause allowing either party to renegotiate terms if the agreement should be reviewed becomes unprofitable may be useful if an exit from the EU is likely to have a substantial impact on the commercial deal.

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The EU – What You Need to Know

EEC, EC and EU

The European Economic Community (EEC) was established in 1957. The Maastricht Treaty, ratified by the UK in 1993, established the European Union (EU). One of the pillars of this new Union, the EEC, was renamed the European Community (EC). The three pillar structure established by Maastricht became one, and the European Union replaced the EC, on the entry into force of the Lisbon Treaty in 2009.

The Internal Market

In 1986, the Single European Act was intended to provide new momentum for the establishment of the common market now called the 'internal market' or single market. The internal market, arguably the bedrock of the European Union, is an area without internal borders designed to ensure the free movement of goods, services, capital and persons: the so-called "Fundamental Freedoms".

The Member States of the EU

The EU has gone through a period of expansion and currently comprises 28 Member States.

The European Treaties

The Lisbon Treaty amended the Treaty on European Union (TEU, also known as the Maastricht Treaty), and the Treaty establishing the European Community (also called the Treaty of Rome) and renamed the Treaty of Rome, the Treaty on the Functioning of the European Union (TFEU).

EFTA

The European Free Trade Association (EFTA) is an intergovernmental organisation set up for the promotion of free trade and economic integration to the benefit of its four remaining Member States – Norway, Iceland, Switzerland and Liechtenstein. A country joining EFTA is not automatically a member of the European Economic Area (EEA).

The EEA

The Internal Market is open to the 28 EU Member States and three of the four remaining Member States of EFTA (Norway, Iceland and Liechtenstein) creating together the EEA. Although the fourth EFTA Member State, Switzerland, is not a signatory to the EEA Agreement, it benefits from a number of bilateral co-operation agreements with the EU. Currently, membership of the EEA is only open to EU and EFTA Member States and a country joining the EU must apply to be a party to the EEA Agreement. The EEA Agreement provides for the inclusion of EU legislation concerning the Fundamental Freedoms throughout the EEA Member States, as well as competition and state aid rules.

EU LAW

EU law is derived from primary legislation (the Treaties) and secondary legislation (such as Regulations and Directives). It is supplemented by the case law of the European Courts (the General Court and the Court of Justice) and general principles of EU law applied by the courts – such as proportionality, legal certainty and subsidiarity – as well as fundamental rights which are increasingly part of primary law. EU law confers either directly or upon implementation into national law rights and obligations in each Member State, as well as on individuals and businesses. The European Communities Act 1972, as amended, provides the mechanism whereby EU law is incorporated into the domestic law of the UK and enables the implementation of changes to UK law. In case of a conflict between EU law and national law, EU law has primacy. When it comes to EU legislation, it is important to distinguish between directives – which have to be transposed into national law – and EU regulations, which are directly applicable across the whole EU. In theory, the latter ought to ensure uniform implementation, which is more effective in removing barriers to trade within the single market. In both cases however Member States' competent authorities – the bodies that police the legal framework – can retain a degree of discretion, meaning there is still scope for differentiation even though the written law is the same.

Additionally, it would be prudent to review contractual termination rights. Consider whether any redefining of the UK's relationship with the EU, could have such a profound effect on any commercial deals that one or both parties should be entitled to walk away. A straightforward way to approach this is to put in place contractual terms that specifically allow for a renegotiation or termination of those agreements following a no vote in the referendum.

Consideration should now also be given to how contractual disputes will be settled. Currently, although each Member State has a different legal and court system with different rules, the European Treaties provide for co-operation between Member States to simplify cross-border judicial processes. If the UK exits the EU, then this framework of EU legislative rules would cease to apply; International Conventions, such as the Hague Conventions, national law and bilateral agreements would determine how conflicts between the rules as applied by different countries are resolved.

Insurance may also be an issue. The terms of existing insurance policies should be reviewed to assess if they cover non-EU exposure and if not, establish if any revised insurance arrangements can be put in place through affordable premiums.

Other Implications

An EU exit, whatever the route, could mean stricter requirements for UK companies in their dealings with personal

> **Inserting a generally worded hardship clause allowing either party to renegotiate terms if the agreement becomes unprofitable may be useful if an exit from the EU is likely to have a substantial impact on the commercial deal.**

data, and it is very likely to impose additional burdens on international organisations trying to deal with compliance across multiple jurisdictions. In dealing with international data transfers, companies would need to review and update contractual terms involving cross border data sharing, such as clinical research arrangements. If the UK left the EU and did not remain in the European Economic Area (EEA) the UK's Data Protection Act would remain in force. However, unless otherwise agreed, the UK would no longer be subject to the Data Protection Directive (Directive 95/46/EC), nor would it benefit from being an EU Member State under this directive.

Organisations transferring personal data (such as health data) from EEA Member States to the UK, including intra-group, could therefore be required to put additional safeguards in place, such as model clauses. It is likely the UK and the EU would reach a pragmatic solution – such as the UK being "white listed", or another separate EU-UK specific agreement being entered into. Additional complications could arise if the proposed General Data Protection Regulation is adopted prior to the UK leaving the EU. Upon a UK departure from the EU the Regulation would no longer apply (and the Data Protection Act is likely to have already been repealed to make way for the Regulation), leaving a gap in domestic legislation that would need to be filled. Leaving the EU could increase UK autonomy and provide an opportunity for UK life sciences businesses to have a greater say in UK data protection legislation. However, this autonomy may be limited by requirements such as white listing (or other equivalent arrangements) encouraging the UK to retain similar data protection legislation to that of the EU in order to maintain an EU compliant status.

In terms of patent registration and enforcement as currently practiced, a complete exit from the EU is likely to have very little impact. Patent law remains largely unharmonised across the EU and is, with a few exceptions,[3] defined by national law and international treaties such as the European Patent Convention (EPC) and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs). The impact would be greater if the Unitary Patent and Unified Patent Court (UPC) system had come into effect. If the UK left the EU (and even if it remained in the EEA), Unitary Patents would not have effect in the UK. Patent protection could continue to be obtained in the UK either via validating European Patents upon grant to have effect in the UK, or by filing UK national patent applications. In addition, in view of the legislative history and the current wording of the legislation establishing the UPC, the UK could no longer participate in the UPC system and the Central Division of the UPC, handling life sciences matters, which under current plans will be based in London, would likely be moved to another Member State.

EU rules govern most aspects of the commercialisation of medicinal

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products including clinical trials, regulatory approval, manufacture, pharmacovigilance, supply, labelling and advertising. If the UK voted to leave the EU but remained in the European Economic Area (EEA) then the regulatory framework for medical products would not change substantially.

However, if the UK were to leave the EU completely, although the UK legislation would probably not immediately change, the UK would have to negotiate mutual recognition agreements in some areas. It might also be expedient for the UK to retain the substance of EU law bearing in mind that where companies are operating and trading within the EEA there would need for continuing compliance with EU law.

If the free movement regime no longer applied this could restrict the talent pool for life sciences and other technology companies based in the UK, and immigration issues could potentially restrict the ability of such companies to form an international workforce.

On the world stage, the EU is a leading actor in pushing forward trade and investment liberalisation. Although both the EU and Member States are members of World Trade Organisation (WTO) in their own right, in practice, within the WTO the EU speaks on behalf of both the EU and the Member States. The EU's ability to strike free-trade deals has been particularly beneficial for the UK's life sciences sector. The EU has successfully negotiated a free trade treaty with South Korea and there are the ongoing negotiations for an agreement to abolish all business tariffs between the EU and US. If the UK were to leave the EU, companies operating in the UK could lose the benefits of these agreements.

The UK is also a net beneficiary from the EU's scientific research funds. In particular, the EU Horizon 2020 Programme is an important source of funding and facilitates cross-border and multi-disciplinary collaboration; indeed having partners based in other Member States is often a pre-condition for accessing EU funding. If the UK were outside the EU, UK companies may not be able to benefit under this programme; recent tightening of Switzerland's immigration laws, which run contrary to conditions for involvement, has affected Swiss participation in Horizon 2020 and European educational programs such as Erasmus.

Although it is beyond the scope of this article, the impact of a future UK exit from the EU on the devolution settlement should be considered. Would it ever be possible for England to exit the EU within a UK in which Scotland, Wales and Northern Ireland remained EU members?

The Ongoing Debate

Possible arguments for the UK renegotiating its relationship with the EU include complaints about ever-tightening regulation. EU legislation can take significant time to negotiate given the need for the agreement of a qualified majority of Member States in most cases. Once legislation is adopted, it can be difficult and time-consuming to amend or repeal. This, it has been claimed, can lock the EU and Member States into a particular policy approach or technological solution that does not easily allow the impact of subsequent policy innovation, new scientific evidence or developments in technology to be reflected. Think of policies such as “information to patients”, the unitary patent package, clinical trials, GMOs, patentability of stem cells, falsified medicines and the ongoing negotiations around new medical devices and data protection legislation.

However, certainty, consistency and an ability to influence are important considerations for businesses in strategic decision-making. EU membership gives UK-based companies access to the single market and a relatively uniform regulatory and legislative system and, whilst the UK is part of the EU, it and businesses operating out of the UK are able to exert some influence over both EU and global regulation. Outside the EU the UK will loose its power to influence but for practical reasons, in some areas, may still be subject to EU law.

On the positive side, there are already signs of change within the EU. There is evidence that the EU is open to adopting a more flexible approach to policymaking. Recognising that Member States often have different perspectives and sometimes require the ability to tailor policies according to their own economic,

> **“The life sciences sector is important to the UK. It is therefore vital that any debate about the UK’s future in Europe takes due account of the views of the sector.”**

cultural and political circumstances, the EU is seeking to strike a better balance between regulatory harmonisation and public sensitivities in the different Member States. For example, EU Member States have recently been given greater power and discretion over whether to allow or prohibit cultivation of genetically modified organisms.

The life sciences sector is important to the UK. It comprises almost 5000 companies with a £56bn trade surplus per year, according to the PWC report, “From Vision to Decision, Pharma 2020”. It is therefore vital that any debate about the UK’s future in Europe takes due account of the views of the sector. Even if the UK pulled out of the EU completely, decisions made in the EU would continue to have a profound effect on the UK and businesses operating out of the UK; the UK, however, would have lost its voice in the debate. Therefore, engagement with and participation in the ongoing national and wider European debate about modernising, reforming and improving the EU is essential.

If the UK votes to leave the EU, it will be important to have a say in how it should leave. Now is the time for an alliance across the life sciences sector to work towards a shared vision of the UK’s place inside or outside the EU.

The UK government launched a Review of the Balance of Competences in 2012.[4] This was an audit of what the EU does and how it affects the UK. The review completed in December 2014, following over two years of evidence gathering and analysis by the government. The House of Lords EU Select Committee has recently reported on its inquiry into the review, [5] and although it welcomed the review as an ambitious piece of work, the inquiry report criticises the government for a failure to draw the 32 reports completed in the review together in a final analysis and for failing to promote the Review effectively. The overall analysis is an essential element if the review is to have an impact on the wider public debate on the UK-EU relationship.

Holding the referendum may give the UK government some advantage in ongoing negotiations about reform of the EU. The Government should, however, also be pushed to produce a final analysis of the Review of Competencies; this could be used to influence any reshaping of the UK’s relationship with the EU in the current negotiations and in any future negotiations post the referendum.

It is proper to end with a quote from David Cameron’s Bloomberg speech on 23 January 2013: “Alone we would be free to take our own decisions …if we leave the EU, we cannot of course leave Europe.”

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Pharma and Biotech Valuations: Divergent Perspectives

Over at least the past decade, risk-adjusted net present value (rNPV) has emerged as the de facto standard for valuing pharmaceutical R&D projects.[1,2] These valuations are used for several purposes including prioritising projects within a portfolio, making investment decisions, valuing a licensing transaction and valuing intellectual property in a sale setting. Controversies remain, not least the choice of discount rate to apply, but the methodology remains very widely used, at least in big pharma and those biotech companies that have not lost faith in rNPV. This paper briefly documents an alternative risk-profiled MC rNPV valuation (rpNPV), and highlights a material divergence between the perspective of a biotech company (with a single or small number of projects) and big pharma (with a broad portfolio).

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Risk-adjusted NPV is Notoriously Fallible

In the context of high – and often unquantifiable – uncertainties inherent on pharmaceutical R&D and market forecasting,[3] it is known that even rNPV techniques provide "misplaced concreteness" whereby "the tendency to overlook uncertainties, margins of error and ranges of probability can lead to damaging misjudgements".[4] The approach is based on standard discounted cash flow (DCF) techniques with future cash flows weighted by the probability of a drug progressing from one development stage to the next. Superimposing Monte Carlo (MC) simulations on to rNPV calculations provides explicit recognition of this and results in an rNPV expressed as a range associated with a specific probability distribution.

Conventional rNPV Valuation with Monte Carlo Simulations (Standard MC Model)

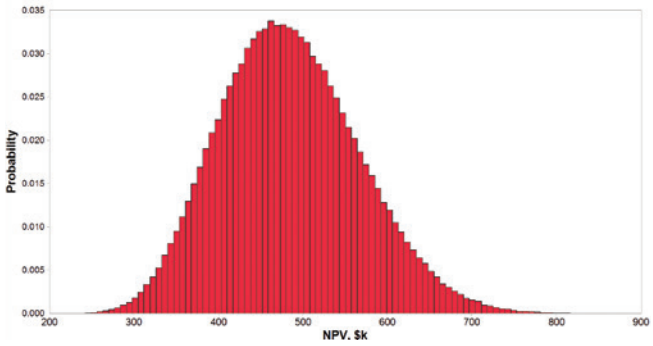
As a practical illustration, consider a novel therapeutic for non-small cell lung cancer (NSCLC) starting phase 1 clinical trials with the basic assumptions as set out in Table 1; uncertainties, especially commercial ones, are very high and reflected by wide input ranges. The probability of progressing from one development stage to the next, using benchmarks that have been widely used in the industry,[5] are assumed to be:

- Phase 1 to phase 2 trials: 71%
- Phase 2 to phase 3 trials: 45%
- Phase 3 trials to pre-registration: 64%
- Pre-registration to product approval: 93%

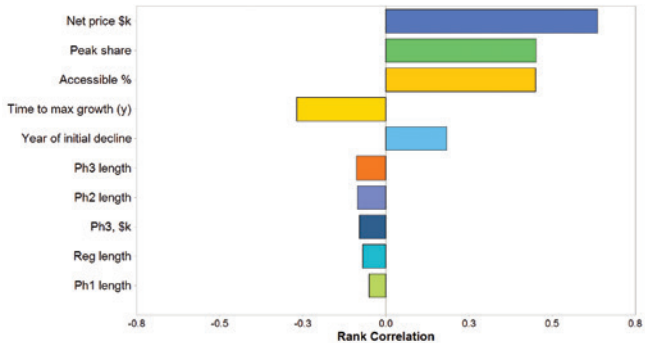
Cumulatively, the probability of technical success, from preclinical development through to product approval, is 19%; many would argue this is overoptimistic relative to contemporary experience, especially in a challenging indication such as NSCLC, but the analysis presented below holds with more stringent benchmarks based on success rates in specific indications and with different technologies (small molecules, biologics, etc.) (data not shown).[6]

In the standard rNPV model, the net cash flow is multiplied by the cumulative probabilities at each stage; i.e. all cash flows from phase 1 to phase 2 are multiplied by 0.71, from phase 2 to phase 3 by 0.71 x 0.45 = 0.32, etc. The formal calculation of rNPV uses a familiar standard algorithm.[7] Using the midpoint values for all the ranges specified in Table 1, at a discount rate of 8% the rNPV = US$485 million. Using the MC method, this calculation is repeated many times (in this example, 50,000 times) using a Microsoft Excel spreadsheet plug-in (Model Risk 5, Vose Software BVBA), each run using a different value in each of

Figure 1: Output of a Standard MC Model



a) The x axis shows rNPV in US$k and the y axis shows the probability for each rNPV value. This distribution is slightly right-skewed, accounting for the small difference between the mean value in this distribution ($484 million) being marginally lower than the non-MC rNPV ($485 million).



b) a Tornado plot showing the top ten input assumption ranges in terms of their impact on the rNPV. This is expressed as a rank correlation between the set of values generated for the output and each input in turn. It is a commonly used form of sensitivity analysis, mostly useful for identifying key variables that should be analysed in more detail. The scale runs from -1 (completely negatively linearly correlated) through 0 (no linear correlation), to 1 (completely positively linearly correlated).

the assumption ranges in Table 1. These 50,000 simulations effectively sample the range of possible outcomes based on an appropriate probability distribution for each input variable. (For most variables, this model used a Project Evaluation and Review Techniques (PERT) distribution.[8])

The mean rNPV from these simulations is $484 million, effectively identical to the non-MC value. More importantly, the range of rNPV values is shown in a histogram plot (Figure 1a), with the 5th and 95th percentiles for rNPV, respectively, being $357 million and $627 million. This probability distribution provides a far richer insight into the rNPV associated with this early-stage R&D project. In this example, all values in the range are positive, but for projects where the commercial target is smaller or the uncertainties higher (data not shown), the first quartile or even more of the rNPV range can be negative despite a positive mean rNPV, clearly providing a more accurate view of the risks involved in pharmaceutical R&D. More importantly still, the relative impact of each range of input assumptions on the outcome of the rNPV calculation is shown in a Tornado plot (see Figure 1b).

Consistent with conventional wisdom, the assumptions with the greatest impact on valuation are:

- Price
- Peak market share
- Accessible market (available market taking into account clinical, payer and other restrictions on treatment eligibility).

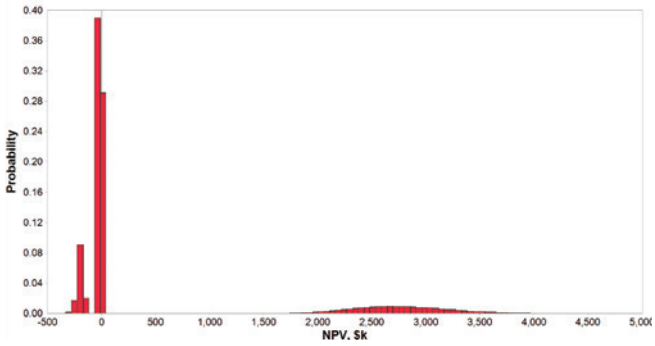
Assumptions such as the cost of clinical trials, even Phase 3, have a significantly lower impact on rNPV. It is precisely this sort of analysis that led many in the industry, certainly up to circa 2005, to focus very strongly on commercial parameters and to invest heavily in clinical development with relatively scant regard for R&D budgets.

While it provides an illustration of the potential spread of project NPVs and the assumptions that the greatest impact on the range, the MC rNPV method still masks the reality of the situation where

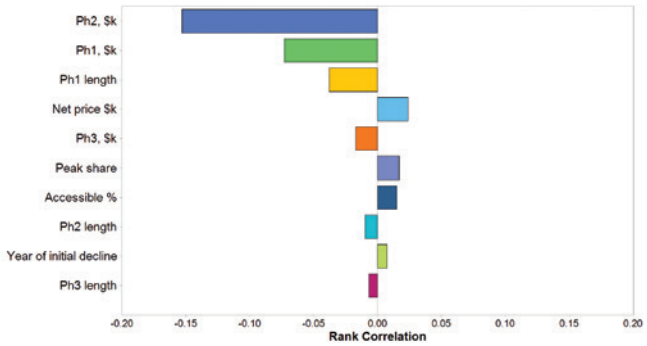
Table 1: Basic Project Assumptions

	Parameter	Assumptions
Development phase	Duration of phase 1 trials	3 – 5 quarters
	Cost of phase 1 trials	$4.0 – 5.0 million
	Phase 2, 3 cost per patient	$100,000 – $120,000
	Duration of phase 2 trials	7 – 9 quarters
	Number of patients in phase 2 trials	275 – 375
	Duration of phase 3 trials	11 – 13 quarters
	Number of patients in phase 3 trials	1,200 – 2,400
	Duration of pre-registration period	3 – 5 quarters
Commercial phase	Launch costs	$75 – 125 million
	Phase 4	$4 million
	Net annual price to manufacturer	$70,000 – 110,000/patient
	Total theoretical patient population	135,000
	Accessible/reimbursed population	50 – 70%
	Peak market share	25 – 35%
	Time from launch to peak sales	3 – 5 years
	Year of initial sales decline	7.5 – 8.5 years post launch
	Time to maximum sales decline	1 – 3 quarters
	Dedicated marketing and sales staff	120 (50% upon sales decline)
	Fully loaded sales/marketing staff cost	$325,000/ FTE/year
	Tax rate	35%

Figure 2: Output of a Stringent MC Model.



a) shows an rNPV probability distribution as shown in Figure 1a. In this case, the distribution is trimodal with the median value being negative (commensurate with the majority of R&D projects failing to reach the market).



b) shows a Tornado plot in the same manner as Figure 1b.

projects more often fail than succeed. As a result it has less utility in decision-making than stringent use of MC methods can provide.

Overcoming the Limitations of the Conventional Approach Using a Stringent MC Model

The fundamental problem with the standard rNPV method is that it applies a probability weighting to cash flows according to transitions through key development hurdles, e.g. it calculates 71% of cash flows from phase 1 to phase 2. In reality, however, there is no such thing as 71% of a cash flow; instead, 29% of the scenarios result in no cash flow beyond phase I (as the trial yielded a negative result), and 71% of the scenarios resulted in a full, not partial, cash flow between phase 1 and phase 2.

To reflect real-life scenarios better, we use a stringent MC model: simulations are run in which 71% proceed beyond phase 1, of which 45% proceed beyond phase 2, of which 64% proceed beyond phase 3, etc. Only 19% of the scenarios have cash flows beyond the pre-registration phase, consistent with the overall probability of the product reaching the market; 81% of the scenarios have negative rNPV.

Using the same project assumptions, the mean rNPV is still $484 million, but the shape of the histogram is radically different (see Figure 2a). In this case, the probability distribution is trimodal; at the fifth percentile with an rNPV of -$202 million, at the 15th percentile with an rNPV of -$34 million and at the 90th percentile with an rNPV of $2.7 billion.

The first peak corresponds to a late-stage development failure. By far the highest peak (the most probable outcome) is the middle one, corresponding to an outcome of a modest loss on a project cancelled at a relatively early stage. The third peak, with a very high valuation is clearly the least probable and reflects a successfully launched new product.

This model is materially more representative of the economics of drug development than the conventional method outlined first, and can therefore arguably claim higher validity. It is not in common use possibly due to the lack of MC simulation expertise and culture within the pharmaceutical and biotech industries.

The Tornado plot for the stringent MC method (Figure 2b) provides a fascinating dichotomy. In contrast to the standard method, commercial assumptions such as price, market share and market access pale in relation to development parameters, namely:

- Cost of phase 2 trials
- Cost of phase 1 trials
- Length of phase 1 trials.

Given that early development is where most projects fail, it is not surprising that these parameters have the highest impact on valuation. Interestingly, biotechs tend to be much better at minimising costs and time of early phase clinical trials than big pharma.

> “In contrast to the standard method, commercial assumptions such as price, market share and market access pale in relation to development parameters.”

> **“The standard rNPV approach does not serve portfolio management well as it always favours short-term and incremental projects at the expense of early stage and strategic projects. Instead, an rpNPV approach should be used to make trade-offs between projects within a portfolio.”**

Risk-profiled NPV

Using the stringent MC method, the shape of the rNPV histogram, together with the parameters of the Tornado plot, constitute a risk-profiled NPV model (rpNPV) which is more representative of the reality of life sciences R&D than standard rNPV values.

The standard method may be germane to a biotech company focusing on a single product or perhaps a small portfolio. It is particularly useful in situations addressing a single asset, such as a partnering transaction, where the Monte Carlo analysis constitutes a systematic, multi-parameter sensitivity analysis. In these situations, the histogram plot output makes explicit the range of value encompassed by the uncertainty in the input assumptions, and the Tornado plot identifies which assumptions contribute most to this uncertainty. This can be useful to focus negotiations onto key parameters rather than those which have little or no effect on the ultimate rNPV number used as the basis for the transaction. It can also be important to guide further analysis and/or market research onto parameters where a narrowing of the input assumption ranges would significantly reduce the uncertainty in the valuation.

However, the probability distribution of the rNPV range using the standard approach does not reflect reality and is materially and consistently overoptimistic. The rpNPV (stringent method), in contrast, reflects the dynamics of a large portfolio of the type present in major integrated pharmaceutical firms or venture capital investors.

The standard rNPV approach does not serve portfolio management well as it always favours short-term and incremental projects at the expense of early stage and strategic projects. Instead, an rpNPV approach should be used to make trade-offs between projects within a portfolio.

Beyond this, a possible message from the rpNPV model is that big pharma should pay maximum attention to containing the costs and duration of early development phases as these have a higher economic impact in the context of a broad portfolio than optimising post-launch commercial parameters for individual products although, obviously, these are not unimportant. A corollary is that it may be economically most efficient for Big Pharma not to conduct early development at all, rather it would maximise shareholder value to acquire products that have already successfully navigated phase 2 proof-of-concept clinical trials. Indeed, many are already some way down this path as they increasingly outsource R&D.

The rpNPV model provides much greater insight/transparency into the dynamics driving project returns, enabling more effective comparison between alternative development paths for a project and between different projects competing for resources where they may have similar standard rNPVs but radically different risk profiles. As such it is a valuable decision-making tool for modern portfolio management.

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Continuing Strength of IPO Market Throws Up Interesting Trends

There is no denying the last 18-24 months have seen an unprecedented uptick in the number of companies rushing to the take advantage of the wide open initial public offering (IPO) window. Between the beginning of 2013 and the first quarter of 2015, 144 companies have come to the market, as new issues have been enthusiastically embraced at a level not seen since the genomics bubble of 2000.

By EP Vantage staff

Those who thought the US$2.96 billion raised on western markets in 2013 would be hard to beat saw that total more than double in 2014, to $6.3 billion, as 87 companies went public. Even Europe managed finally to get in on the act with 13 flotations in 2013 coming from the continent. But this figure does mask the fact that notwithstanding UK-based Circassia recording one of the biggest IPOs in biotech history, more than half of the Europe-based companies chose to chance their luck in the more vibrant US market.

An indication of the just how buoyant the market has become is that when the first quarter IPO tally on western exchanges in 2015 only totalled $783 million it was seen as disappointing. However, investors with longer memories might want to recall that even this "meagre" figure was only $178 million shy of the $931 million raised in the whole of 2012 (see Figure 1).

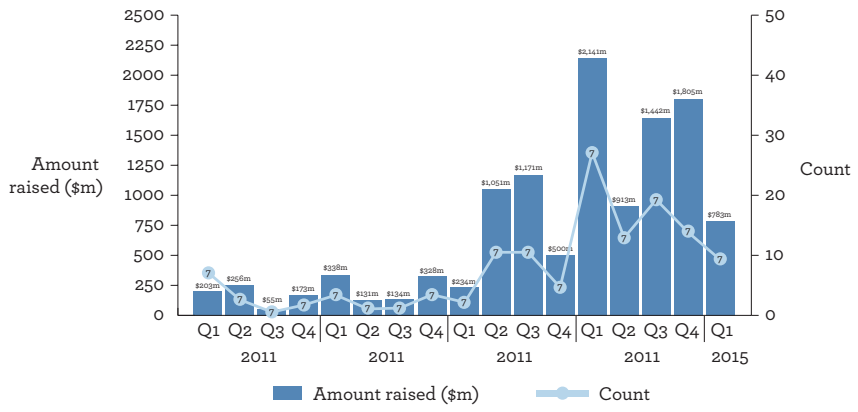
As such, this recent dip in flotations might not be cause for concern just yet and could simply be down to natural fluctuations in IPOs by quarter, or to the sheer number of biotech companies which decided to take the plunge in the final quarter of 2014, leaving few prepared to float in the New Year 2015.

In addition, this March saw a market wobble that, although not as significant as 2014's, could have discouraged companies with shelf registrations from following through. And the big medical meetings that tend to liven up biotech sentiment, like the European Association for the Study of the Liver (EASL) meeting and American Society of Clinical Oncologists (ASCO) conference, occur in the second quarter.

What did get away, however, was of pretty good quality. The average discount to the guided price range for floats on the all-important Nasdaq exchange was 7%, just missing out to the third quarter in 2013, on being the lowest quarterly 'haircut' of the current IPO window, and across all exchanges it was 2%. This was in stark contrast the regular 20% plus reductions in guided price to float price that we saw back in 2012 and 2013 (Table 1).

The share price rise so far looks healthy compared to 2014's IPO crop, although

Figure 1: Biotech initial public offerings on Western exchanges (excludes medtech). Source: EP Vantage & Evaluate Ltd



> **If you are a preclinical biotech seeking an IPO, alongside a buoyant market, what appears to really help is having the right VCs behind you.**

there is plenty of time left for setbacks that could make that number look a little less impressive.

First quarter 2015 biotech IPOs on Western exchanges are summarised in Table 2. The big float was Spark Therapeutics, which was the beneficiary of renewed interest in advanced treatments like engineered T-cell therapies. In Spark's case, the one-time antipathy towards gene therapy has disappeared and in its place it found $185 million in funding for its pipeline of assets for eye, blood and central nervous system disorders.

The enthusiasm did not end with its size: on its first day the shares doubled, and at the end of the quarter Spark's stock was three times its IPO price, its market cap is now over $1.5 billion.

While Spark gets the award for the biggest float in Q1, the biggest premium went to FlexPharma, which specialises in treatments for severe neuromuscular conditions. At the other end of the spectrum, Inotek Pharmaceuticals took the biggest haircut at 57%.

Impressively, European companies represented six of the 13 IPOs in Q1. This perhaps confirms UK fund manager Neil Woodford's strategy of preferring European biotechs because of the high valuations of their US counterparts.

No Clinical Assets, No Problem

Aside from the sheer amount of money raised in the last year or so, and the opening of the window in Europe, a deeper dig into the data reveal there have been other striking trends in the IPO market. Perhaps most notable is the number of US companies which have managed to IPO with few, or in some cases no, products in the clinic.

One of the most recent examples of this was Blueprint Medicines, the oncology-focused biotech floated on Nasdaq in April, it had yet to test any of its projects in a single patient, but this did not stop it from pricing above its range, raising $147 million and enjoying a first-day share price bump.

While this might seem counter-intuitive, and that later stage de-risked companies would be obvious IPO candidates, a look at recent flotations using *EvaluatePharma* data, show that Blueprint was not alone in treading this premature path.

More surprisingly, the analysis also shows that a lack of any clinical-stage assets does not appear to be a huge impediment to the success of a biotech at IPO, either in terms of amount raised or valuation uptick (see tables below).

That said, flotations of companies with only preclinical assets remain a rarity. Our analysis, which includes IPOs from the start of 2013, the beginning of the bull run, until the end of the first quarter of 2015, show only four such early-stage entrants. To put this into context, during the same period 100 biotechs listed on western exchanges.

The bull market has undoubtedly helped preclinical companies get off the ground, as the crop of later-stage investments had pretty much all got

Table 1: Nasdaq premium discount to IPO price range since 2012

Period	Average
Q1 2012	(26%)
Q2 2012	(31%)
Q3 2012	(21%)
Q4 2012	(17%)
FY 2012	(24%)
Q1 2013	(23%)
Q2 2013	(12%)
Q3 2013	(6%)
Q4 2013	(31%)
FY 2013	(15%)
Q1 2014	(9%)
Q2 2014	(18%)
Q3 2014	(16%)
Q4 2014	(9%)
FY 2014	(12%)
Q1 2015	(7%)

Table 2: Q1 2015 biotech IPOs on Western exchanges (all Nasdaq unless stated)

Company	Date	Amount Raised	Premium/ (Discount) to Range	First Day Close	31 March Close
Zosano Pharma	January 27	$57m	0%	0%	(8%)
Ascendis Pharma	January 28	$124m	6%	5%	(4%)
FlexPharma	January 29	$99m	23%	(7%)	23%
TRACON Pharmaceuticals	January 30	$41m	(23%)	(6%)	40%
Spark Therapeutics	January 30	$185m	15%	117%	237%
Poxel1	February 06	€25m ($28m)	(10%)	8%	67%
Bone Therapeutics[1]	February 06	€32m ($37m)	3%	0%	37%
EyeGate Pharma	February 13	$5m	(14%)	0%	(42%)
Inotek Pharmaceuticals	February 18	$46m	(57%)	0%	(10%)
Nordic Nanovector[2]	March 23	NOK500m ($61m)	2%	8%	18%
Redx Pharma[3]	March 27	£15m ($17m)	-	0%	(1%)
OSE Pharma[4]	March 30	€21m ($24m)	15%	(3%)	(10%)
Cerenis[1]	March 30	€53m ($58m)	15%	(3%)	0%
	Average	**$60m**	**(2%)**	**9%**	**27%**

[1]Euronext, [2]OSE, [3]LSE AIM, [4]AMF

away, and investor demand seemed at times to outpace supply. This has had the consequence of pushing companies onto the market at much earlier stages of their development.

Friends in the Right Places

But if you are a preclinical biotech seeking an IPO, alongside a buoyant market, what appears to really help is having the right VCs behind you. A case in point is Agios Pharmaceuticals, whose private backers included Third Rock Ventures. At the time of its 2013 float it had a cancer metabolism-focused pipeline that was still at the preclinical stage.

In the event Agios floated at well above its price range, securing an average 228% valuation increase for its private backers, and currently stands up some 450% on the IPO price. Already having Celgene as a partner helped it rise, as did the subsequent reporting of impressive clinical data at last year's American Society of Hematology conference last year.

But the Third Rock link is interesting. Third Rock also backed Blueprint, whose float is not included in this analysis since it occurred after the end of Q1. Despite not have any clinical assets it is now worth $750 million, and a look at filed S-1 documents shows pre-IPO investors got an average 176% valuation gain at float.

Of the four preclinical-stage new issues in this analysis (Table 3), only ContraFect is currently trading below its IPO price. And news in April that the anti-infectives company had moved into clinical trials with its lead product failed to lift the shares, which have been steadily drifting downwards.

But notwithstanding ContraFect and the low number of preclinical-stage IPOs in general, the 141% average post-IPO performance of the four companies that had no clinical assets when they floated is remarkable. Investors must already be on the lookout for the next preclinical-stage Third Rock float.

The Business You Are In

Alongside stellar returns for risk-loving investors willing to fish in preclinical waters, our analysis also shows that de-risked phase 3 assets also provided a decent return for investors, with the 23 companies with pivotal assets enjoying an average 88% rise in share price since IPO. The poorest returns were those for companies with phase 2 assets (see upper section of Table 4).

If post-IPO performance by therapy area is examined (lower section of Table 4), it is not surprising to see the white hot

> "Perhaps most notable is the number of US companies which have managed to IPO with few, or in some cases no, products in the clinic."

Table 3: Braving the public markets with no clinical assets

IPO Date	Company	Amount Raised by IPO ($m)	IPO Price Range	IPO Offering Price	Average Share Price pre-IPO	Valuation Bump Up at IPO	Share Price Change Since IPO
18/09/14	ProQR Therapeutics	112	$11.00-$13.00	13.00	4.09	218%	95%
29/07/14	ContraFect	41	$5.00-$6.00	6.00	4.31	39%	-14%
24/07/13	Agios Pharmaceuticals	106	$14-$16	18.00	5.49	228%	424%
30/01/14	Dicerna Pharmaceuticals	90	$11-$13	15.00	10.43	44%	60%

**Between 2013 and end of Q1 2015. Source: EvaluatePharma, SEC filings.*

area of oncology leading the way in average cash raised at float and post-IPO performance. Companies operating in anti-infectives have also not fared too badly, and investor interest might have been driven by the increasing concern over growing antimicrobial resistance. The 12 companies falling into this category, which includes Intrexon, Pfenex and Adamas Pharmaceuticals, have on average managed to rise 31% after flotation.

VCs Celebrating the biotech IPO bump

As our previous analysis has shown, floated biotechs have rewarded their IPO investors handsomely across all development stages. But what of the early-stage backers of these US market debutants?

As both S-1 filing information and data from EvaluatePhama show, equally impressive is the valuation step-up received by mere virtue of moving to the public markets. Companies that have floated since the beginning of 2013 saw an average a valuation rise of 150% the day of their public premieres, which should be a satisfying reward for venture.

As can be seen from the information in Table 5 (next page), the jump in value is spread fairly broadly throughout the sector, with some therapy areas as usual benefiting more than others.

A surprise is that the IPO bump performance of preclinical companies is not especially different from that of those with phase 2 or 3 candidates at IPO, which has been a sign of how groups with both attractive valuations and assets have been hunted nearly to extinction in the biotech boom by venture investors.[x]

However, the fact that companies with preclinical assets tend to perform better post IPO says more about the nature of the bull-market, than the investment decisions of venture investors.

Sweet Spot

Of course, it helps to be in the industry sweet spot: an oncology company raising $100 million or more. On average the latter attribute is worth nearly a quadrupling in market valuation at IPO, while the former doubles it. But some groups even in the comparatively un-sexy CNS and anti-infectives spaces have benefited.

That is not to say there have not been some duds: Globeimmune, whose work

Table 4: IPO performance by development stage and therapy area

	Average Amount Raised by IPO ($m)	Average SP Since IPO*	No. of Companies in Analysis
All IPOs**	81	52%	100
Phase 3 companies***	94	88%	23
Phase 2 companies****	81	39%	55
Phase 3 + 2 companies	85	53%	78
Pre-clinical companies	87	141%	4
Oncology companies	87	48%	23
CNS companies	55	15%	11
Systemic anti-infective companies	67	31%	12

as at end Q1 2015; **2013 to Q1 2015; * whose most advanced asset is in phase 3; ****whose most advanced asset is in phase 2.*

»

Table 5: Pre- and post-IPO valuation splits, by development stage and therapy area

	Average Amount Raised by IPO ($m)	Average Share Price pre-IPO	Average IPO Offering Price	Average % Bump Up at IPO	Average SP Since IPO	No. of Companies in Analysis
All IPOs	81	7.46	12.22	150%	52%	100
IPOs that raised $100m+	147	5.64	18.11	294%	96%	24
IPOs that raised $80m+	125	6.68	16.44	222%	100%	39
IPOs that raised $40m+	88	7.43	12.65	136%	62%	89
Phase 3 companies	94	8.25	12.7	158%	88%	23
Phase 2 companies	81	7.69	12.32	148%	39%	55
Phase 3 + 2 companies	85	7.85	12.43	151%	53%	78
Pre-clinical companies	87	6.08	13	132%	141%	4
Oncology companies	87	8.55	12.83	105%	48%	23
CNS companies	55	6.12	10.27	115%	15%	11
Systemic anti-infective companies	67	11.57	10.83	43%	31%	12

**Through end of Q1 2015. Source: EvaluatePharma and SEC documents*

spans both oncology and anti-infectives, saw its valuation shrink 70% at IPO and it has not come close to recapturing any of its previous glory. Another anti-infective group, Scynexis, dropped 68% in value with its IPO.

On the other hand, CAR-T play Kite Pharma has to be seen as the undisputed champion of the investor chase, its valuation rising 507% at IPO and shares rocketing another 239% afterward. Fellow CAR-T player Juno Therapeutics may be looking on with a tinge of jealousy, as it managed just a 411% increase in valuation at IPO and has eked out a 153% gain since.

What Have You Done for Me Lately?

Broadly, the post-IPO performance has been healthy, with a 52% rise in share price. EP Vantage has noted the comparative performance of the four preclinical groups in this analysis with their lower-risk, late-stage brethren. But as with the IPO step-up, all sectors have been broadly on the increase with oncology and the biggest IPOs pulling the train.

CNS groups stand out in this metric as the most disappointing – a relative term – with just a 15% average share price increase through the end of 2015's Q1. But double-digit increases are more the norm on this measurement than with the IPO bump-up, with only the $80 million-plus IPO and preclinical categories managing anything greater than a doubling in share price.

With performances like these, it is no wonder so many biotechs have fallen for the allure of the public markets, perhaps driven by their backers noting returns others have been receiving.

But as the debate rages over whether the sector is in a bubble, the question for those companies that have not jumped is whether they are already too late to capitalise – a question that stubbornly private groups like Intarcia Therapeutics need to consider.

Biotech Cassandras have been proven wrong repeatedly in this boom, but it is a truism that the good times will have to end sometime. Expect Q2 IPOs to be watched closely as investors try to determine whether the first three months were a mere blip or a sign of things to come.

Reference

1. "No clinical assets? No problem." EP Vantage, May 8, 2015.

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How Pharma Underestimates the Sales of its Top Products

Pharma companies are good at identifying the products that will become big successes at the time they launch them. But they wildly underestimate how successful these products will become. It is not that companies have failed to identify them as future successes. It is just the sheer scale of the success that they fail to fathom.

By John Ansell, Senior Partner, TranScrip Partners

Over the past decade I have become increasingly aware of a widespread phenomenon – the underestimation of the prospects for new products that become major successes.

I decided to look at top-selling global products. Let's first see how forecasters fared with the top five globally best-selling products of 2013 (see Figure 1), in reverse order. (Note that The IMS rankings in Figure 1 are based on aggregated sales for products from around the world, marketed under different names or by different marketing companies. In contrast, Figures 2 and 3 are based on ex-company sales.)

All but one of the main companies marketing these five products provided forecasts at or around the time they were launched.

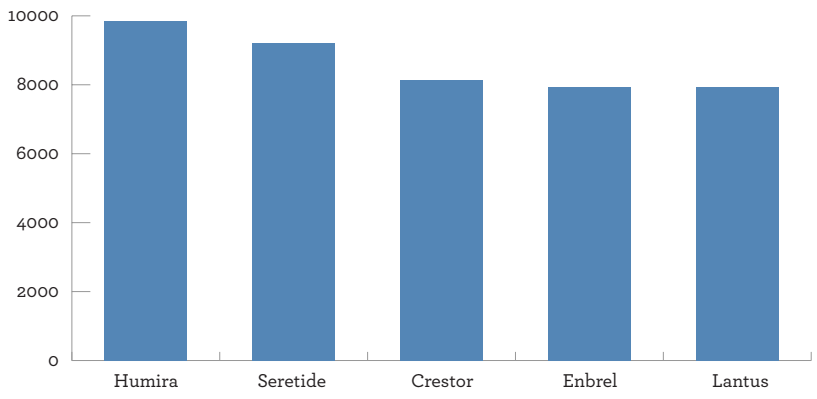
Fifth Place: Lantus

Aventis (now Sanofi) launched Lantus (insulin glargine) in its first market in 2000. Just prior to this, Aventis estimated that peak sales would reach US$500m. By 2013 they had reached a remarkable $7.935bn: over 15 times that forecast.

Fourth Place: Enbrel

Enbrel (etanercept) was first launched in 1998. In a press release the year before, the product's then owner, American Home Products, highlighted Enbrel as one of four new products it believed to have worldwide sales potential in the $500m to $1bn range. By 2013 sales had reached $7.949bn. Thus the company was out by a factor of at best nearly eight times and at worst nearly 16 times.

Figure 1: Top five global products 2013 sales ($ thousands)



About the author

John Ansell has been an independent pharma consultant since 1990, advising pharmaceutical companies, start-ups and other companies in a wide range of areas including international marketing, business development and licensing. In 2012 John became a Senior Partner at TranScrip Partners.

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Figure 2: Crestor global sales ($ billions)

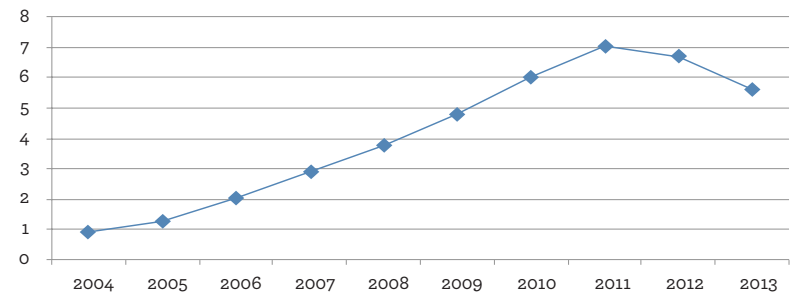
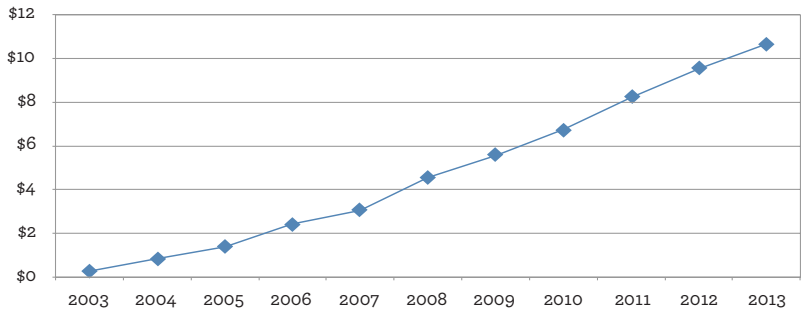


Figure 3: Humira global sales ($ billions)



Not long after launch, American Home Products paid a penalty: it was unable to fulfil demand and so curtailed promotion of Enbrel whilst it built additional factories.

Starting from a first indication in rheumatoid arthritis, Enbrel gradually gained indications in a range of related indications, including psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis. No doubt the broad indications eventually registered helped sales to go way beyond initial expectations.

Third Place: Crestor

AstraZeneca did not reveal forecasts for its statin Crestor (rosuvastatin) at the time of its launch in 2003. But bank analysts mostly produced peak forecasts in the range of $3-3.5bn. One, ING Financial Markets, went slightly farther in predicting sales of $3.6bn in year five. AstraZeneca sales of Crestor turned out to reach just $3.0bn in that year. Within the short time horizon projected by these banks, they appear to have been reasonably accurate.

But that was not the end of the story. After year five, sales continued to climb, reaching a peak of $7.055bn in 2011 for AstraZeneca's brand, as shown in Figure 2. By comparison, the IMS audited sales in Figure 1 show that total sales for all rosuvastatin brands peaked a year later, at $8.215bn). Thus the forecasts at launch were mostly under half of the eventual peak sales level.

More importantly from a commercial standpoint, almost three quarters of total Crestor sales occurred after year five. The sales occurring in this phase of the product's lifecycle were therefore not just an additional bonus; this has been the period when the majority of total sales have occurred. Crestor is a good example of the limitations of inadequate forecasting timescales, particularly as essayed by financial institutions. Beware of consensus forecasts derived from short-term bank estimates like those made for Crestor.

Second Place: Seretide

When it was first launched in 2001, Glaxo expected Seretide (fluticasone + salmeterol; marketed as Advair in the US) to reach sales of between £1bn and £2bn per annum. By 2013 sales were $9.213bn (IMS data), or £5.906bn. Glaxo was therefore not as dramatically far out as some of the other top-five

» “Aventis estimated that peak sales would reach US$500m. By 2013 they had reached a remarkable $7.935bn: over 15 times that forecast.”

Table 1: Top products by global sales in 2014 with their rankings in 2013

Product	2013 Rank	2014 Rank	2014 Sales $bn	% Growth vs 2013
Humira	1	1	11.8	22
Lantus	4	2	10.3	30
Sovaldi	-	3	9.4	>999
Abilify	7	4	9.3	19
Enbrel	5	5	8.7	11
Seretide	2	6	8.7	-5
Crestor	3	7	8.5	6
Remicade	8	8	8.1	8
Nexium	6	8	7.7	-1
Mabthera	9	10	6.6	4

Source IMS Health

» product companies. But, at the upper and lower limits of its forecasting range, the company still underestimated sales by nearly three to just under six times.

Number One: Humira

In 2003 Abbott expected Humira (adalimumab) to achieve sales of more than $1bn. This level was reached within two years of its first launch (Figure 3). Sales then went on to reach a massive $10bn in 2013 ($9.851bn according to IMS audited data in Figure 1;$10.659bn according to Abbott, Figure 3), or ten times the basic blockbuster threshold Abbott expected to surpass.

Humira is another example of a product whose sales have grown as new indications have been added. Currently there are no less than seven approved indication areas. But this was largely anticipated at launch by Abbott. All but one of these indications, ulcerative colitis, were projected for development at the time Abbott launched the product. Such an indication roll-out is becoming the rule rather than the exception for currently successful products.

In the first six years on the market (2003-08), aggregate Humira sales were $12.591bn. In the five years since (2009-13), aggregate sales were $40.734bn, well over three times as much. Just as with Crestor, the bulk of total sales come from the latter years on the market.

Whilst discounting cashflows reduces the impact of sales from later years on the market, the importance of their contribution during a product's lifecycle is very clear from the above examples.

Thus forecasts that are limited to the first few years on the market are near-worthless in assessing the full commercial impact a product is likely to have. Yet many banks continue to be reluctant to give more than five-year forecasts, not realising that pharmaceuticals is quite unlike most other leading industries for which they project forecasts.

Conclusions

None of the launch forecasts for the top five products came anywhere near being accurate. Moreover, the sales of some of them had not obviously peaked by 2013. Therefore the extent of their ineptitude is likely to prove even greater in some cases.

How do these findings compare with past examples? In 2006 and again in 2013, I examined a number of products whose intellectual property rights had recently become exhausted.

Formerly, companies were less forthcoming than they have subsequently become about publicising expectations for their products at the time they launch them. Thus I relied more often in these earlier analyses on forecasts at launch published by financial institutions. The products I found forecasts for included Nexium and Abilify, which in 2013 IMS still ranked respectively as the number six and number seven best-selling products. Other major products included Zyprexa, Aricept, Plavix, Singulair and Lipitor. You can view the 2013 data in a presentation on line.[1]

I found a similar picture then as I did for the current top five products, with peak sales almost always at least five times forecast levels, and the majority eight or more times. There was an interesting outlier, Lipitor, which was clear champion at 25 times. Moreover, in 2013 I was unable to find any long-term forecasts for other major products that were more accurate. Thus the overall picture was much the same as with the current top five products. Forecasting skills therefore show no improvement.

Why Under-Forecasting?

Apart from the reasons I mention above, what else goes to explain under-forecasting? I discuss the psychology of under-forecasting in detail in my book Transforming Big Pharma.[2] Briefly, there are far more reasons to under-forecast than to over-forecast.

Regarding over-forecasting, start-up companies may be tempted to exaggerate commercial potential in order to impress potential investors, but they are often soon found out if they try to do this. And there are few other motivations to do so.

Set against this are a whole variety of reasons for companies to under-forecast:

- They may not be very aware at launch of the potential of their products across multiple indications
- They may feel it is "safer" to be cautious in forecasting to avoid any investor backlash if sales underperform and earnings per share are affected
- There can be a lack of imagination about future potential:
  - the price levels that might be commanded
  - often for a relatively uncharted indication, difficulties in realising the scale of potential
- Lack of accountability: rarely will a forecaster be called upon to account for an inaccurate long-term projection. With normal staff movement and turnover, the timespan is just too long
- Overestimation of existing market satisfaction.
- To reiterate – and very much last but not least – the sheer underestimation of the potential lifespan of a product. As I have found, the longevity of a top 50 global product – that is, duration from first launch to peak sales – remains on average 13-14 years, much above that assumed in most forecasts.[2]

2014 Rankings

New successes are emerging. Are forecasters any more successful at predicting their sales? Look at Gilead's hepatitis C product Sovaldi (sofosbuvir), which was first launched late in 2013. 2014 sales turned out to be not far short of $10bn, ranking it at number 3.

Yet even at the time Sovaldi was launched in December 2013, a survey of fund managers conducted by International Strategy & Investment Group showed that they expected peak sales to be around $3bn in 2014. Some commentators considered that Gilead was paying over the odds when it paid $11bn in 2011 to acquire Pharmasset, the company which developed Sovaldi. Gilead appears to have been rather shrewder than the investment banks in its expectations for Sovaldi, though it made public no forecasts at launch.

Table 1 shows that to replace Crestor and Seretide, which had fallen out of the top 5 by 2014, Sovaldi was accompanied by the second newcomer, Abilify (aripiprazole, Bristol-Myers Squibb).

At the time of its launch in 2003 the market intelligence company ICIS projected sales of $1.4bn for 2007 and suggested that the product was not capable of having a major impact on Bristol-Myers Squibb's sales growth. Once again, the dangers of short-termism in forecasting are embarrassingly evident. Abilify's 2014 sales at $9.3bn were 6.6 times this predicted level and are still growing strongly. Quite clearly it has been a key contributor to Bristol-Myers Squibb's recent performance.

The Pitfalls of Under-Forecasting

There are several consequences of under-forecasting:

- Most obviously, as we saw with Enbrel, a product can simply go out of stock.
- Where companies seriously underestimate the full potential of their upcoming products, they may turn their attention to an unnecessary extent to alternative corporate strategies, such as diversification or M&A. They may at the same time give insufficient priority and resources to supporting their own products.
- Companies – and the pharma industry as a whole – stand to attract insufficient investment when they undervalue their assets.

For many years the pharmaceutical industry kept growing despite a longstanding dearth of new products. With hindsight we can now see that one important factor which pulled the industry through was that major products performed far better and for far longer than the companies marketing them usually expected. It's time for companies to step up the effort and expertise they put into forecasting thereby ensuring that they make the most of the next generation of new products.

References

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2. *Ansell J. "Transforming Big Pharma – Assessing the Strategic Alternatives." Gower Publishing, 2013.*

Deal Watch

Almost half way through the year and May has seen a slightly top-heavy Deal Watch Table with two corporate acquisitions with headline values of over US$8bn. However, this month saw the smallest number of corporate acquisitions in the year to date, when compared with the previous months in 2015. The aggregate value of the top 20 deals was also down from the previous month where we reported the high value AbbVie/Pharmacyclics acquisition at $21bn.

By Sharon Finch, Medius Associates

Topping the table with a headline value of $8.4bn was the acquisition of Synageva BioPharma by Alexion. The deal comprises cash and shares with a premium of +140% over the closing price on May 5, 2015. This agreement brings access to Kanuma (sebelipase alfa) which is in registration for the treatment of lysosomal acid lipase (LAL) deficiency. The number of late-stage opportunities in the rare diseases space is fairly limited so this represents a significant step forward for Alexion. Staying with rare diseases, Cortendo closed a deal with Antisense Therapeutics for ATL 1103 in acromegaly. Making an upfront payment of $5m, the deal carries milestones of $105m for the phase 2-ready asset.

With a similar headline value to Synageva/Alexion and building on its acquisition plans was the purchase of Par Pharmaceuticals by Endo. It has proven a busy year for Par with the Auxillium acquisition closing in January followed by the on-off planned purchase of Salix (Salix was successfully sold to Valeant for $14.5bn in February). Clearly the money was burning a hole in the Endo shareholders' pockets and this will consolidate the company's position in the generics field.

Staying with the generics topic, the ongoing saga of Teva – Mylan – Perrigo has gone quite quiet with the various parties indicating that the negotiating gap is fairly far apart. There will no doubt be lots of backroom activity, for example, Mylan investor Paulson & Co has increased its stake to 4.5% – some 22 million shares. Wellington Management also followed suit adding a further 12.5m shares moving up to a 6.5% share of the business. But clearly Teva has had some other issues to consider. One of the potential down sides of acquisitions is that significant risks may be acquired with the assets. This has proved to be the case following Teva's purchase of Cephalon in May 2011 for $6.2bn which brought Provigil (modafinil for sleep disorders) into the portfolio. The product has been the subject of an investigation from the US Federal Trade Commission (FTC) and, although not usually reported in Deal Watch, the $1.2bn settlement is noteworthy recognising the higher price paid by patients due to the delayed availability of generics. This is not the first such case for Teva, as the FTC also filed suit last September for an alleged pay for delay relating to AndroGel. This will all be good practice for Teva as there will be considerable antitrust activity if the Teva-Mylan deal goes ahead.

De-risking - Exercise of Options

Another feature which has emerged strongly in the deal landscape is the use of options, and this month saw two companies move ahead and exercise their option rights. Firstly, Boehringer Ingelheim progressed its deal with the Australian company Pharmaxis acquiring PXS4728A in phase 1 for non-alcoholic steatohepatitis. PXS4728A is an oral treatment which inhibits SSAO/VAP-1. Valued at $600m, Boehringer Ingelheim has paid an upfront fee of $31m with a further $63m in milestone payments linked to the start of phase 2 and phase 3 clinical trials and a further $160m in regulatory

> **Lilly has recently seen a return to the Deal Watch commentary and May saw the company build further on its long standing relationship with Transition Therapeutics with the out-licence of the phase 2-ready selective androgen receptor modulator TT701.**

milestones. Similar payments are available for any second indication that emerges from the programme; royalties are payable in the high single digits.

Emanating from the initial co-development agreement signed with Selecta in 2012 Sanofi has exercised its option to an exclusive licence to develop an immunotherapy for the treatment of coeliac disease. Selecta is eligible to receive fees up to $300m per allergen indication (a maximum of three giving a total deal potential of $900m) with double digit royalties on commercial sales.

Oncology – Yet Again!

With the high number of oncology deals that have closed this year so far, the trend simply continues with a further five deals being concluded this month. Interestingly though, it is not always the major players as evidenced by the deals between bluebird bio with Five Prime Therapeutics, and Editas with Juno Therapeutics.

The Editas/Juno collaboration brings together the Editas CRISPR/Cas9 genome editing capabilities with Juno's expertise in immuno-oncology. Editas received an upfront of $25m with a further $22m in research support; milestones of $230m per programme plus tiered royalties. It was a busy month for Juno who also closed a deal with Fate Therapeutics. Financial terms include an upfront of $5m with Juno buying equity of $8m, $50m in milestones with low single-digit royalties. Juno will also provide funds for the four-year collaboration.

This collaboration focuses on identifying small molecules to modify T cell product candidates to improve therapeutic potential. Last in its hat trick of deals this month was Juno's acquisition of Stage Cell Therapeutics for an initial payment of $59m with $150m in success payments. The acquisition provides access to transformative cell selection and activation capabilities.

Almost all of the companies with oncology interests had bought into CAR-T / immunotherapeutic approaches with the possible exception of Lilly. This omission was rectified this month as Lilly closed a deal with BioNTech. The research collaboration will identify novel tumour targets; BioNTech received a $30m upfront fee with a further $300m in milestones plus tiered double digit royalties. In addition Lilly is making a $30m equity investment.

Lilly has recently seen a return to the Deal Watch commentary and May saw the company build further on its long standing relationship with Transition Therapeutics with the out-licence of the phase 2-ready selective androgen receptor modulator TT701 to Transition. Lilly receives a contingent $1m upfront, with up to $100m in milestones and single-digit royalties. The deal flow with Lilly reaches back to March 2008 with Transition's gastrin-based therapies (potential disease-modifying therapies for patients with diabetes) including the lead compound TT-223. Under this agreement, Transition received a $7m upfront, with up to $130m in milestones, as well as royalties. Both parties participate in the clinical development in T2 diabetes.

On to June 2013 and Lilly exercised its option to develop and commercialise the anti-diabetic drug candidate TT-401. In an interesting deal structure, Transition received a $7m milestone and the agreement was amended so Transition would contribute $14m to Lilly over the course of the phase 2 clinical study. In return, if successful, Transition would then receive an additional $240m in milestone payments plus double-digit royalties. This was quickly followed in July 2013 when Transition secured an exclusive global licence of worldwide rights to TT-601 a phase 1 ready novel small molecule transcriptional regulator for the treatment of osteoarthritis. Lilly retained an option to reacquire rights to TT-601 following the PoC study results. If exercised, Transition would receive $130m in milestones and a high single-digit royalty. If not exercised, Lilly is in turn, eligible for a low single digit royalty from Transition. Clearly a very successful and creative partnership!

Choosing to opt for partnership over an acquisition, J&J closed a multiple licence with Achillion to build on its hepatitis C portfolio. The agreement covers ACH 3102, ACH 3422 and sovaprevir. The intention is to trial a combination of ACH 3102 with a NS3/4A HCV protease inhibitor plus an NS5B HCV polymerase inhibitor. ACH 3102 has been granted fast track designation by the US FDA. The deal includes an equity investment of $225m plus milestones of up to $1.1bn and tiered royalties.

Keeping in the headlines, Pfizer secured a minority interest in the »

Deal Watch – July 2015

Licensor Acquired / Licensee Acquirer	Deal Type	Product/Technology	Headline $m
Synageva/ Alexion	Corporate acquisition	Rare diseases portfolio including Kanuma (sebelipase alpha) for LAL deficiency	8,400
Par/Endo	Corporate acquisition	Generics business	8,050
Sorrento (Igdrasol)/ NantPharma	Asset acquisition	Acquisition of Igdrasol including Cynviloq (paclitaxel nanoparticle)	1,300
Achillion/ J&J	Licence	Joint development and commercialisation of ACH 3102 [P2], ACH 3422 [P1], sovaprevir in hepatitis C	1,100
Sigma Tau/ Baxter	Asset acquisition	Oncaspar (pegasparagase - marketed) portfolio in acute lymphoblastic leukaemia (ALL)	900
Editas/Juno Therapeutics	Collaboration	Development of next generation CAR-T and TRC cell therapies using CRISPR/ Cas9	737
AM Pharma/ Pfizer	Acquisition of minority interest	Exclusive option to remaining stock, access to recombinant human alkaline phosphatase	600
Pharmaxis/ Boehringer Ingelheim	Exercise of option to acquire	PXS4728A for non-alcoholic steatohepatitis (NASH)	600
BioNTech/ Lilly	Research collaboration	To identify and validate novel tumour targets and corresponding T cell receptors	360
Aspen/ Strides Arcolab*	Divestment	Range of branded and generic drugs	301
Selecta/ Sanofi	Exercise of option to exclusive licence	Development of an immunotherapy treatment in coeliac disease	300
Retrophin/ Sanofi	Acquisition of priority review voucher [PRV]	For Cholbam [cholic acid] in bile acid disorders	245
Prosonix/Circassia	Corporate acquisition	Portfolio of generic respiratory products including fluticasone	152
Isis/ Bayer	Licence agreement	Anticoagulant ISIS FXI Rx for prevention of thrombosis in P2	155
Antisense Therapeutics/ Cortendo	Licence agreement	To develop and market ATL 1103 [P2 ready] in endocrine disorders including acromegaly	110
Five Prime/ bluebird bio	Licence agreement	For development of CAR-T cell therapies	130
arGEN X/ Leo Pharma	Licence agreement	For access to an antibody in inflammation based skin conditions in preclinical development	116
Arena Pharmaceuticals/ Roivant Sciences	Licence agreement	For Nelotanserin, a 5-HT2A receptor in P2, in behavioural and neuropsychiatric disturbances	105.5
Eli Lilly/ Transition Therapeutics	Licence agreement	For TT701 a selective androgen receptor modulator in P2 for androgen deficiency	101

**Australia and Singapore*

company AM-Pharma with an option to purchase the remaining equity in the company. The option is exercisable on completion of the phase 2 studies in acute kidney injury related to sepsis. The purchase included an $87.5m upfront with $512.5m on exercise of the option. Following the collaboration announced in June 2014 with Cellectis, the rumours are now going around that Pfizer may be planning an acquisition with an estimated price tag of $1.6bn. Watch this space!

PRVs

Finally, we noted in the Annual Deal Watch report for 2014 the emergence of the trade in priority review vouchers (PRVs). A PRV is a transferable asset issued by the FDA to a company which obtains approval for a treatment in a neglected disease.

Sanofi has been adept in this area with its previous access to a PRV for Alirocumab for dyslipidaemia (in partnership with Regeneron who had originally purchased the PRV from Biomarin) for which together they paid $67.5m in July 2014. Sanofi purchased the paediatric PRV from Retrophin for the total consideration of $245m ($150m on closure with two subsequent payments in 2016 and 2017 of $47.7m). The paediatric PRV was issued when Cholbam was approved for the treatment of patients with peroxismal disorders.

Overall, May proved to be quite an eclectic mix of deals, not only with PRVs but a wide range of therapeutic fields — CVS, CNS, respiratory, dermatology and rare diseases; it will be interesting to see what the summer has to offer!

2015 EUROPEAN PLG EVENTS

PLCD 'Chat at the Fireside'
Tuesday 15th September
Gendarmerie, Berlin

XII International Pharma Licensing Symposium (XII IPLS)
Wednesday 16th - Friday 18th September
Hilton Berlin

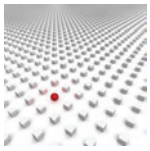
PLG Spain XV General Assembly
Thursday 1st & Friday 2nd October
Hesperia Hotel, Córdoba

PLCD Aufbauseminar
Monday 5th - Wednesday 7th October
Hilton Berlin

PLCF Presentation & Discussion
Thursday 15th October
Cercle Interalliée, Paris

PLG UK Workshop & Drinks Reception
Thursday 15th October
Fasken Martineau Offices, London

NPLG Autumn Networking Dinner
Thursday 29th October
Skodsborg Hotel, Copenhagen



PLG UK Introduction to Healthcare Business Development Training
Monday 16th - Wednesday 18th November
Marriott Lingfield Park

PLCF Breakfast Presentation
Tuesday 17th November
Cercle Interalliée, Paris

Italy HLG Autumn Meeting & General Assembly
Thursday 19th & Friday 20th November
Milan

PLCF Training Session (Part 3)
Thursday 3rd December
Cercle Interalliée, Paris

PLG UK Workshop & Christmas Drinks Reception
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