Big Pharma's Bad Attitude

Pharma has been big news with politicians and public wading into industry debates and it has come out on the losing side its accomplishments forced into the shadows (p8)

Expert View

Deloitte, Roland Foxcroft shares his view on how to build partnerships with digital leaders to create mobile apps that satisfy all stakeholders (p20)

Stockwatch

Politicians may not yet be able to distinguish between inflation of generic drugs and the high prices of innovative and recently launched drugs, the debate and rhetoric will polarize (p21)

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UK Bioscience In Frontline Of EU Brexit Revenge

JOHN HODGSON john.hodgson@informa.com – 28 June 2016

Although the UK vote to leave the European Union has caused immediate uncertainty and resentment, the actions of a spurned EU desperate to deter other nations from leaving could soon hit UK-based researchers hard.

Two working days after the UK voted to leave the European Union, many of those at the research end of European life sciences were still in shock. Brexit's impact on the research community remains undefined and neither the British government nor the European Union authorities have yet issued any assurances.

Carlos Caldas, a leading cancer researcher based at the Cancer Research UK Cambridge Institute, was recently award a €2.5m Investigator Award from the European Research Council (ERC). He has not yet received confirmation from the ERC that the award will stand although he assumes it will because "the money is already committed." However, he noted that the situation may be less clear for colleagues based in the UK who are applying for the latest round of ERC awards.

That uncertainty is "typical of the disastrous nature of the whole [Brexit] affair," said Caldas. It's easy to believe that research matters are not the first priority for the UK government right now, he said, "although they should be because innovation and the academic system is a very important to the UK."

"There is anger, anxiety and fear," said Rolf Apweiler, co-director of the European Bioinformatics Institute in Hinxton, near Cambridge, UK. In one incident after the referendum, local people accosted off-duty EBI staff to say, "We voted you out, so why are you still here?"

The Brexit vote appears to have emboldened that kind of xenophobic spite, something that Apweiler believes impacts the morale of all staff at EBI, whether UK-born or foreign. It is one of the indirect effects of the UK decision and, he says, a major challenge for EBI along with recruitment, and participation in collaborative projects.

Direct funding for EBI will be unaffected because it is not an EU body: rather it is supported through the European Molecular Biology Laboratory, an intergovernmental organization with separate international agreements.

"There will be some additional administrative burden in hiring people from the EU," said Apweiler, "but we need to make it clear that we can manage that process with potential staff and their families, and that EBI can continue to be as active in EU-funded collaborations as it has ever been."

EBI may escape the direct impacts but, according to Claire Skentelbery, UK research activities in general are unlikely to be immune. Skentelbery is a researcher with Scientists for EU, a pro-EU social media campaigning group. With over 128,000 members on FaceBook, Scientist for EU has argued in the UK media, in *Scrip* and on its

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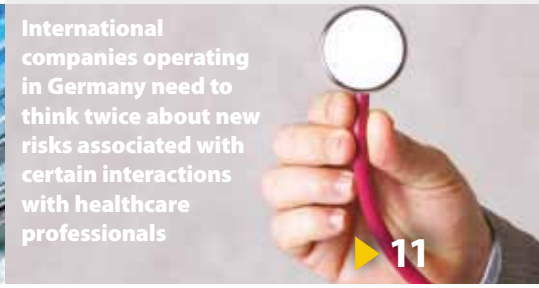

from the editor

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Scrip is expanding the breadth and global reach of our content for members of the global biopharma commercial community.

Starting on July 11, *Scrip*, PharmAsia News and Start-Up will be amalgamated to bring readers of all three publications more in-depth insights into commercial developments in the global biopharma market. The new service will retain the Scrip name and all current subscribers to one or more of the three brands will have immediate access to it.

By joining forces and delivering the full content stream on the new platform that we launched in April, we are creating an outstanding business intelligence service drawing on hundreds of years of cumulative experience gained by our international team of journalists while reporting on the issues that affect our readers all around the world.

You will continue to receive the insightful analysis and in-depth coverage that readers of each product rely upon. But now, you will get it all in one place.

There will be additional information and instructions on the launch day, Monday July 11. Online and PDF readers of this notice can also click to read our fact sheet.

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Brexit: The Implications For Biotech Fundraising And Investment

UK biotech's concerns following the Brexit vote in the EU referendum center around the impact on financing, regulation and personnel, Scrip learns through conversations with a number of industry leaders.

SUKAINA VIRJI sukaina.virji@informa.com – 29 June 2016

Brexit. Hardly anyone outside the UK saw it coming. In fact, many of those who actually voted for the UK to leave the EU were surprised by their victory. But while the UK's political system flails around like a beached whale, business leaders are trying to keep a calm head.

"As a bank, a lot of our clients deal with ambiguity on a daily basis and while [the result] was disappointing in some respects, it doesn't change their plans or their business to a large degree," Nooman Haque, director of healthcare and life sciences with Silicon Valley Bank's UK Branch, told *Scrip*.

And with the resignation of prime minister David Cameron and the ensuing reluctance to instigate Article 50, which would set the ball rolling on extracting the UK from the EU, the only thing that is certain in these times is uncertainty.

"In particular there is a lot of uncertainty over what will happen to European sources of funding, such as Horizon 2020 [the biggest EU research and innovation program which has nearly €80bn of funding available over seven years]. The EIB (European Investment Bank) and EIF (European Investment Fund) act as investors in venture capital funds. What their role will be going forward for UK based VCs is unsure," he said. "In the short term uncertainty will affect fundraising and investment."

However, "One thing about biotech is that it is resilient and the fact is that the UK has a strong base which should be able to attract funding in any situation. Scientific credibility doesn't disappear overnight. Expertise doesn't disappear overnight."

CURRENCY VOLATILITY

The real issue is the volatility in the value of sterling, according to Haque. While it has regained some of the ground lost following the June 23 referendum result, there is a long way to go before overseas investors feel secure enough to negotiate deal terms.

"My expectation is that where deals are currently ongoing, they are almost certainly going to take that little bit longer. I would expect that that until we see some sort of stability in the value of the currency."

Haque also acknowledges there will likely be an effect on personnel. "Not a huge effect, because there is an acceptance that anyone who is already here is going to be allowed to remain here. But from the scientific community, both academic and commercial, there is a concern that if the sentiment around immigration really takes hold then it could deter clever people, from across Europe especially, from wanting to base themselves in the UK."

Kate Bingham, managing partner at venture capital firm SV Life Sciences, is another calm head in the storm.

"With regards to immediate effects [of the Brexit vote], it's going to be in terms of financing and can we attract money into our companies. In the longer term it's going to be about how to get innovative medicines to patients in the UK and is a Brexit going to harm that, and the answer is … maybe."

Kate Bingham

Bingham's concerns fall under three banners: financing, clinical and regulatory, and people, but she sees a few potential silver linings.

"Obviously currency volatility is a problem, and that's going to put investors off from either investing in VC funds or coming into UK companies, at least until it's all settled down. It may be that with a rapid change in leadership, the currency will settle down, but that's probably not for 6 to 12 months."

She noted that raising public money will be a challenge, but "it always has been challenging in the UK."

'BUREAUCRATIC AND PAINFUL'

Haque among others cited concerns over access to EU grant funding. Bingham is not too concerned here. "Our companies haven't really used much of that because European money has been always bureaucratic and painful. It's certainly never been a material part of any company we've ever invested in," she said.

She believes this is a good opportunity for the government to think more sensibly about where to put its money. "If the UK can now focus its science budget funding to be more targeted to key areas of interest here [in the UK] then actually that may well be good, rather than waiting for handouts from Europe which I don't think have been particularly well targeted, certainly not for the UK."

Bingham noted that some UK based VCs will have the EIF as a significant investor, "and that's going to leave a hole."

She is also expecting to take a hit to the valuation of portfolio companies, "but I am not going to worry about minor depreciations. If a company is successful … it isn't going to be too painful."

While fundraising from outside of the UK might prove tricky in the short term (or longer), Bingham wouldn't be surprised to see an upswing in other types of deal-making. "The UK is a lot cheaper now, so in terms of M&A, I wouldn't be surprised if we do start seeing some because that sort of depreciation is actually pretty interesting for acquirers."

A possible positive from Bingham's point of view is the potential for removal of the AIFMD (Alternative Investment Fund Managers Directive). "What it says is that you can't go and fundraise in any country in Europe without having a passport and jumping through hoops; it's very intrusive and asks you to report on stuff that in our sector is difficult to do."

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LOSS OF INFLUENCE

Jim Van heusden

On the clinical and regulatory side, Bingham's main concern is the loss of influence the UK would have on European clinical trial directives as the EMA will have to relocate from its London headquarters. "That is a shame because [European clinical trial directives] may not be perfect but they are not that bad. And there are some elements of European regulation that are better than the US. Maybe we can opt in like Norway to certain directives, but for sure our influence is eliminated. That's a negative."

However, there is a glimmer of a silver lining. The accelerated access review is under consideration by the UK government "and that's all about bringing new medicines into clinical trials and then to market much more quickly here in the UK, so it may be that not having to comply with all these European rules will enable that to take off more quickly and be more effective."

'ISOLATIONIST BRITAIN'

However, on the personnel side, Bingham said it's all negative. She shares many of Haque's concerns.

"A lot people on my senior management teams are European nationals. That ability to attract and retain good international talent will be harder. And if you think about science and innovation and entrepreneurship, it all depends on an open and collaborative exchange of ideas and people and approaches. Isolationist Britain is not a good thing for that. "

And then there are the question marks. "Where will we end up with IP (intellectual property)? The current system works just fine. Do we get excluded from that?"

These concerns are shared by those outside the UK. Jim Van heusden is CEO of Sweden's Karolinska Development, and a former venture capitalist.

"The general feeling over the continent is that nobody expected this result," he told *Scrip*. "When I first heard, I thought it was a joke."

UMBRELLA AGREEMENTS?

He believes that there is potential for the life science sector in the UK to be significantly impacted by the decision to leave the EU. "What you really don't like as an investor is uncertainty. If UK companies want access to funds from outside the UK, there is a lot of risk. We don't know how regulatory processes will be handled in the future, for example. We don't know if they will fall under the EMA umbrella or not." Van heusden noted that Norway and Iceland work under umbrella agreements "but people will want clear answers before doing an investment," he warned.

"In the end it might be like the Millennium Bug. A lot of talk about it and then in practice not a lot will change for the sector. But no doubt quite a number of agreements need to be negotiated and put in place."

However, he sounds a positive note. "There is a lot of money already available within the UK. And if that proves tough, UK people are very welcome to come and set up companies in Sweden."

Van heusden feels sorry for the people that are in the mid stages of raising a financing round. "I wouldn't be surprised if people were to just walk away from the deal until they have further clarity."

'PEDAL TO THE METAL'

On this note, David Ebsworth and the management team at Verona Pharma are breathing a huge sigh of relief. A week before the referendum, the company raised £45m through a conditional placing with new and existing investors, including UK, UK and European healthcare funds.

"It was pedal to the metal to get the deal done before June 23 in case this happened," Verona's chair Ebsworth told *Scrip*. The proceeds of the fundraising are being used to progress RPL554 through a Phase II testing. He is very disappointed at the decision to leave the EU. "We had extensive discussions with the [UK regulatory body] MHRA about the clinical development program. Now we're asking ourselves if we need to go and speak to a couple of other [European] agencies. Life has become more complicated."

Stéphane Boissel, CEO of French biotech TxCell, believes the negative impact will be much wider spread than just inside the UK. The withdrawal of the UK from the EU will be "a disaster, and no good for the relatively small European biotech sector when compared with, say, the US biotech sector," he told *Scrip*.

CLINICAL TRIALS COSTS

For TxCell, that is conducting clinical studies in the UK on its cell therapies, the cost of that research will go up by 30% after the UK leaves the EU, because it will lose tax credits on UK research costs that it receives from the French authorities. The loss-making R&D company currently receives a cash rebate on research costs generated in the EU to help its development, worth 30 cents for every dollar spent. "At the end of the day, if I can find the same quality elsewhere, we will avoid doing clinical studies in the UK," Boissel noted.

> 'The general feeling over the continent is that nobody expected this result... when I first heard, I thought it was a joke'

"Europe is also channeling a lot of money into collaborative research programs, to encourage European companies and academic laboratories to work together, and UK biotechs and academia will no longer be part of those programs," he added. According to Boissel, it will likely make no sense for the UK to continue to take part by providing new funding, as one of the supposed reasons behind Brexit is to reduce the amount the UK spends on EU projects.

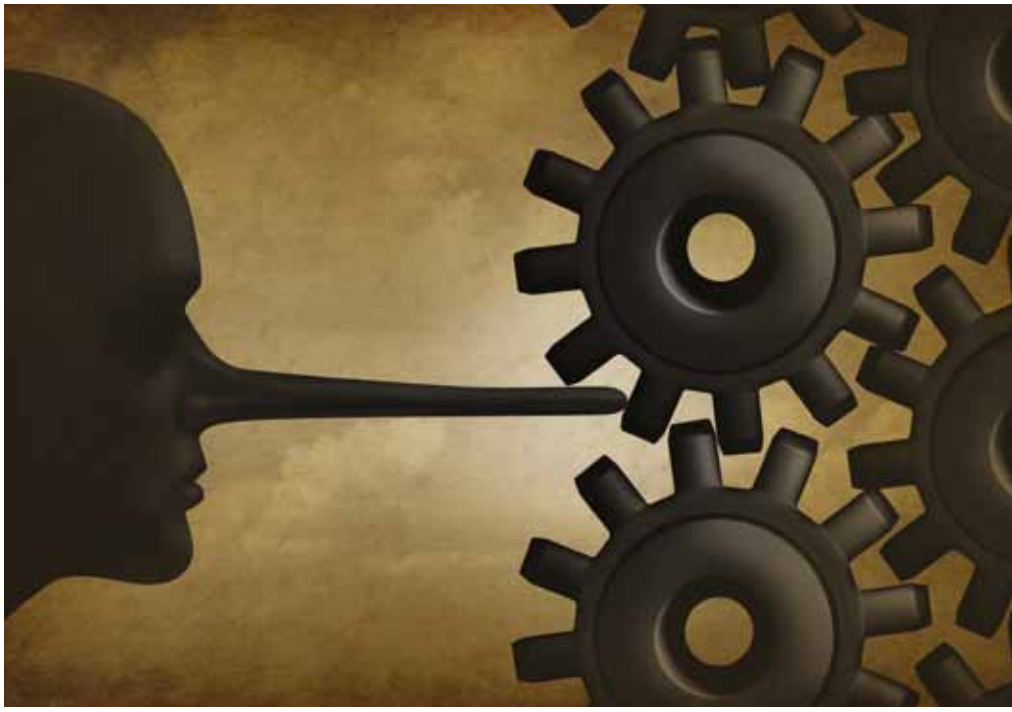
But with regard to investors and venture capital, Boissel is more upbeat. "What matters for these people is the quality of the science and the people, and I don't expect those to change," he said.

Still, what the French executive is going to miss about the UK is "British pragmatism," although he couldn't put a price on the sentiment. "We have learnt a lot from the UK, including for example health technology assessment and NICE, but these are difficult to quantify," he commented.

ABPI Suspends Astellas UK

The UK industry body the Association of the British Pharmaceutical Industry (ABPI) has suspended Astellas UK as a member for one year following serious breaches of its code of practice for the pharmaceutical industry.

ALEX SHIMMINGS alex.shimmings@informa.com – 27 June 2016



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The suspension is in connection with a number of serious breaches of the code, including Clause 2 which deals with actions likely to bring discredit upon, or reduce confidence in, the pharmaceutical industry, and is reserved for use as a sign of particular censure. The actions were sparked by an anonymous complaint from a health professional who was invited to a large advisory board meeting the company held in Milan in February 2014 at which Astellas presented the benefits of its prostate cancer treatment *Xtandi* (enzalutamide) for a then-unlicensed indication (namely for the treatment of men with metastatic castration-resistant prostate cancer who were asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy). The complainant alleged that Astellas was not truthful as to why delegates had been invited to the meeting and the company promoted something it should not have done.

The matter was compounded by a second complaint apparently made by an Astellas employee about the truthfulness of Astellas's response to the original complaint to the Prescription Medicines Code of Practice Authority (PMCPA, the body established by the ABPI to operate its Code of Practice for the pharmaceutical industry independently of the ABPI) – it transpired that Astellas Pharma Europe Ltd. had knowingly provided incorrect information to the PMCPA.

The interim case report AUTH/2780/7/15 for the second complaint says: "The complainant stated that it was extremely alarming and concerning that the account given to the PMCPA was knowingly false and intentionally misleading. In its response to [the initial case, AUTH/2747/1/15], Astellas claimed that all invitees were identified and grouped based on their 'clinical expertise' and 'experience of treating patients with mCRPC' (metastatic castration-resistant prostate cancer). Unfortunately, nothing was further from the truth and Astellas knew that but deliberately chose to conceal it from the PMCPA."

Subsequently, the PMCPA Appeal Board reported the companies to the ABPI Board. The PMCPA Appeal Board was extremely concerned about the multiple organizational and cultural failings, which included issues of deception and imposed additional sanctions. The ABPI board agreed, suspending Astellas UK for 12 months. The companies will both be re-audited in September and these audits "must show demonstrable improvements in both companies – Astellas UK and Astellas Pharma Europe – particularly in relation to corporate culture," the ABPI said. Its board will see this report and review the length of the suspension before the end of 2016.

> The complainant alleged that Astellas was not truthful as to why delegates had been invited to the meeting and it promoted something it should not have

In response, Astellas said it took its responsibilities to uphold the letter and spirit of the ABPI Code of Practice very seriously and accepted fully the decision of the ABPI Board of Management.

"Astellas believes that a strong compliance governance and framework is essential and a comprehensive plan has been in place over recent months to create and maintain a culture where compliance, ethics and integrity are embedded and reinforced at all levels within the organization," it stated.

"Astellas is committed to achieving the required standards of compliance necessary for APL to have its membership to the ABPI reinstated."

Aetna: Entresto's Label Enabled Outcome-Based Risk Share

TIJANA IGNJATOVIC tijana.ignjatovic@datamonitor.com – 29 June 2016

Including the impact on hospitalizations in the label for Novartis's heart failure drug Entresto was critical to enable execution of outcome-based agreements. Such deals present an opportunity for pharma and payers to work together, but many challenges remain.

Speaking at NextLevel Pharma's Spring PharmAccess Leaders event, Aetna's national medical director Ed Pezalla said that Novartis AG's success in including reductions in hospitalizations on Entresto's FDA label was critical in enabling outcome-based risk-sharing deals to be penned for the drug. Having recognized that it faced an uphill struggle in competing against generic standard of care, Novartis talked to lots of different payers in the US and decided it had to go the extra mile and design the trials in such a way that resource utilization data could be included on the label, Pezalla said.

> Cost is going to push insurers to not accept newly approved drugs on the basis of lack of sufficient evidence

Payers, he added, were usually supportive when it came to creating safe harbors for outcomes deals but that pharma companies were often too worried that the FDA might still go after them for off-label promotion, and this is something that hinders the wider use of outcomes-based risk-sharing deals. A legal change to allow inclusion of outcomes outside the FDA label in reimbursement deals and communication with payers would make it considerably easier to engage in risk sharing, he added.

Getting Aetna and Novartis to come to an agreement on how value should be measured was key to the design of the Entresto's risk-sharing deal, Pezalla said. Rather than penalizing Novartis for every hospitalization patients on Entresto experience, Aetna will look at patients' utilization of hospital days as compared with the previous year, and compare the reduction to that observed in Entresto's clinical trials, with reimbursement based on hitting a target based on a sliding scale that changes from one year to another. Only those hospitalizations where heart failure is listed as a cause of the hospitalization will be considered in the analysis.

Pezalla highlighted that while outcomes-based risk-sharing deals were not necessarily going to save money for the payers, with pharma taking on little risk at the moment, they presented an opportunity for pharma and payers to work together to carry out a real-world study to generate data on resource utilization that can inform future reimbursement conditions, as well as optimize patients' treatment.

However, smaller healthcare insurer Harvard Pilgrim Health Care's chief medical officer, Michael Sherman, recently warned during ISPOR (International Society For Pharmacoeconomics and Outcomes Research) that finding the right drug for a value-based, risk-sharing agreement and the right pharma partner to work with would be challenging. Harvard Pilgrim reached a value-based deal with Novartis for Entresto on June 28.

US PAYERS ARE INCREASINGLY LOOKING FOR VALUE, EMPLOYERS COULD DRIVE VALUE-BASED FORMULARIES

Approval of multiple drugs through accelerated regulatory routes will also necessitate wider use of outcomes-based reimbursement deals or coverage through evidence development especially when such drugs come with an expensive price tag.

"Cost is going to push insurers to not accept some newly approved drugs on the basis of lack of sufficient evidence" added Pezalla. And it is in such instances of products approved based on surrogate endpoints without final outcomes data, that ability to use HEOR data outside of the FDA label that may prove to be most valuable. Pezalla urged drug manufacturers to bring forward data on impact on quality adjusted life years (QALYs), and importantly on healthcare resource use efficiency, and to bring them when coming onto the market not later.

He highlighted that insurers are actively looking at improving efficiency, by for example removing pressure on scarce resources such as freeing up hospital beds, and drugs that involve such value propositions are more likely to resonate with payers.

Not many US payers look at value brought by drugs through the cost per QALY prism, at least not systemically or openly, but with the rise of the influence of the Institute of Clinical and Economic Review and the general shift to greater healthcare system efficiency, such health technology evaluation methods look set to expand, albeit slowly.

Pezalla mentioned Premera's Value-Based Formulary as one rare example where an insurer has gone all out and made decisions on a drug's placement on the formulary not based on its price but cost per QALY. Although there are absolute coverage thresholds, the payer uses a drug's wholesale acquisition to place drugs in a tier, with a set cost per QALY threshold for each tier, taking into account rebates where available. Pezalla highlighted that Premera was able to offer this formulary to its self-insured clients, a market segment where the formularies do not have to meet all of the local insurance regulations. For their fully insured programs, insurers are more tightly regulated by the state insurance commissions, making expansion of such value-based formularies more likely in the employer-insured segment. But the onus is now on the employers' willingness to adopt wider use of value-based formularies or payment systems. Pezalla contends that there is little willingness among employers to be a first mover, as not many have taken up more restrictive formularies such as the Express Scripts National Formulary.

Ed Pezalla was one of the speakers at NextLevelPharma's Sprint PharmAccess Leaders Forum held in London on April 26-28, 2016.

CONTINUED FROM COVER

website that Britain need only look to what happened in Switzerland to understand how quickly and detrimentally the European Union may act.

In February 2014, voters in Switzerland narrowly came out in favor of limiting immigration. Subsequently, Swiss authorities had to inform the European Commission that it could not sign a free movement accord with then-new EU member Croatia. The Commission promptly suspended Swiss participation in two major EU science programs, Horizon 2020 and Erasmus. Despite emergency negotiation to regain partial access, the number of projects involving Swiss research institutes dropped to a third of its previous number in a year as their reputation as partners declined.

The official word from the Erasmus program is that the impact of the UK vote "is not clear at this early stage." A statement from Jo Johnson, UK Minister of State for Universities and Science, said that referendum had no immediate effect on applications to Horizon 2020 and that "UK access to European science funding will be a matter for future discussions."

According to Skentelbery, restriction on free movement of EU citizens (which is part of what Britain has voted for) is likely to be a trigger for rapid action. The fact that other EU nations are considering their own referenda places additional political expediency on the situation. "If I was a European Union wishing to emphasize the consequences of an EU withdrawal clear to wavering Dutch and French politicians," she said, "I would act quickly and severely. The Swiss government was shocked at the magnitude and speed of the EU's response. The British government shouldn't be."

How Brexit poops UK parties

- Fewer invitations. Uncertainty over long-term participation makes UK research groups less attractive as partners in EU projects. There is evidence of a huge impact in Switzerland following its immigration referendum despite its excellent science base; a slight drop in UK participation has already been evident in since the UK referendum was announced in 2015.
- Duller guests. Ambitious academics may no longer see a move to the UK as a good career move because of the reduced chances that they can lead multinational science projects from a UK base. Personal considerations may also weigh in: relocating your family is a greater risk if your career faces an obvious block or your partner's job prospects are limited.
- More hosting needed. Shunned UK universities (and companies) should act as coordinators of European funding applications. This implies a greater administrative burden, but also more control ("Take Back Control" was a motto of the Leave campaign).
- Bouncers filter guests. Migrations controls actually prevent some prominent scientists from pursuing a career in the UK and dissuades others from exploring the possibility. Distaste for origin-based selection keeps the high-minded away.
- Authorities ban parties with bouncers. Selective admission policies for EU researchers trigger exclusion of UK institutions from coordinating collaborations under EU programs such as Horizon 2020.
- Second-rate fare. Reduced access to international programs makes UK science largely a national enterprise. Internal competition replaces international enterprise. The objective quality of research, ability to create global intellectual property, start-ups and competition in business relationships are eroded in the long term.
- Action moves to exotic locations. UK biotechs and other small and medium-sized enterprises establish legal bases in other EU countries, especially to anglophone nations with active inward investment policies such as Ireland, the Netherlands, Belgium, Germany and Sweden. Multinationals quietly ensure their ability to participate in international programs by transferring key projects outside the UK.

100 More Jobs Cut At Infinity After AbbVie Inevitably Ends Partnership

MANDY JACKSON mandy.jackson@informa.com – 29 June 2016

AbbVie unsurprisingly walked away from its partnership with Infinity after disappointing Phase II results for the PI3K inhibitor duvelisib. Another 100 Infinity employees will lose their jobs as the company conserves its cash and amends its clinical trial plan.

Infinity Pharmaceuticals Inc. has cut 100 more jobs in the wake of its disappointing Phase II DYNAMO clinical trial for the PI3K inhibitor duvelisib in indolent non-Hodgkin lymphoma (iNHL) now that the inevitable has happened: AbbVie Inc. exercised its right to end the companies' collaboration to develop the drug.

Cambridge, Massachusetts-based Infinity said it would lay off 58% of its staff in light of what was described as a mutual decision to terminate their 2014 agreement, since the company and AbbVie could not restructure their partnership in a way that benefitted both parties. The additional layoffs are on top of a 21% reduction, or 46 job cuts, that were disclosed two weeks earlier when Infinity revealed the DYNAMO results, which showed response rates that were not competitive with other recently approved iNHL therapies.

With AbbVie and its milestone fees for duvelisib's development and commercialization out of the picture, Infinity is trying to preserve its cash for development of the drug and a follow-on compound. The company received a $275m upfront payment from the big pharma in 2014 and $130m in 2015 out of $530m in potential milestone fees.

Even Now, Hope Remains For Duvelisib

Infinity still plans to submit a new drug application (NDA) to the US FDA in the fourth quarter of 2016 based on the DYNAMO data and interim results from the ongoing Phase III DUO clinical trial in the treatment of small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL) with duvelisib or Novartis AG's CD20 inhibitor Arzerra (ofatumumab).

Big Pharma's Bad Attitude: Are CEOs Giving Industry A Bad Rep?

Big pharma has been big news recently, with politicians and the general public wading into industry debates on drug pricing, profit-making and trial transparency under the gleeful eye of the international press. Unsurprisingly, pharma has come out on the losing side of these debates, its scientific accomplishments forced into the shadows by the actions of executives such as Martin Shkreli, who have ensured that the spotlight is firmly on the people behind the businesses rather than the products they manufacture.

SARAH WEIR sarah.weir@informa.com – 1 July 2016

Shkreli is only one example of the "bad actors" which Kenneth Frazier condemned earlier this year in his chair's opening speech at the annual meeting of the Pharmaceutical Research and Manufacturers of America (PhRMA). Frazier, CEO of Merck & Co. Inc., used his speech to highlight the impact of these individuals, stating that "the problem is not just that the actions of a few are soaking up all the attention … it's that so many are convinced that the egregious conduct of these outliers is an accurate representation of our industry."

> 'Pharma's dismal reputation is a real concern for everyone. It lays fertile ground for anti-vaccine conspiracy theorists, quacks, and anti-medical cranks the world over.'

It is not only Frazier who credits the power CEOs wield in influencing perceptions of pharma: in a Twitter poll carried out by *Scrip* last week, 60% of respondents indicated they believe CEOs play a "very important role" in shaping opinions of their companies and the industry as a whole. The repercussions of CEOs' actions can be felt throughout the world of pharma, not merely at a localized level.

With this in mind, it is easy to see how pharma has developed such a degenerate reputation, especially when one considers characters such as Shkreli and Valeant Pharmaceuticals International Inc.'s former CEO, Michael Pearson, both of whom have come under intense public scrutiny for their pricing policies. Nor is this phenomenon merely restricted to pharma: Edelman's 2016 Trust Barometer found that globally, only 47% of the general population trust CEOs to do what is right. The same research found pharmaceuticals to be the only healthcare industry for which trust has declined, indicating that the onus is now on pharma CEOs to claim accountability for their companies' images.

WHAT'S IN A REPUTATION?

How exactly is this CEO-led reputation formed? Ed Coke, director of consulting services at the Reputation Institute, puts it down to actions, rather than words: "CEOs are judged more by the culture they create and the responsible behaviours they engender across their company as a whole, alongside the efficacy of the therapies they develop, rather than their own personal appeal." The decisions leaders make define them and subsequently their companies in the eyes of the general populace and their consumers.

With the industry and its ethics under increasingly close examination, its reputation appears to be more unstable than ever before. The 2016 Pharma RepTrak report published by the Reputation Institute saw 37% of survey respondents rate the reputation of the international pharma industry as "excellent," but another 35% rated it as "weak/poor." This mixed response suggests that a more balanced approach to public image is needed, one which can no longer purely rest on the life-saving work done by scientists.

Whilst the matter of reputation may seem to be a lot of fuss over something which does not directly affect day-to-day operations, smart CEOs will recognize the importance of cultivating a strong reputation. As Ian Read, CEO of Pfizer Inc., pointed out in a LinkedIn "influencer" post, "a bad reputation breeds suspicion," something the pharma industry already struggles with after years of bribery accusations, hidden trial results and back-room dealings, which have resulted in well-publicized court hearings and costly pay-outs.

It is not only the business side of things that suffers: a poor impression of pharma is dangerous for patients too, Dr Ben Goldacre argues. The Bad Pharma author told *Scrip* that in his opinion, "Pharma's dismal reputation is a real concern for everyone. It lays fertile ground for anti-vaccine conspiracy theorists, quacks, and anti-medical cranks the world over."

TREATING BAD PHARMA

There are glimmers of hope for pharma's image though. Last year, Lars Sørensen, CEO of Novo Nordisk AS, was named by the Harvard Business Review as the best-performing CEO in the world. The secret to his success? Sørensen attributes it to a combination of teamwork, honesty and grounding, combined with some good, old-fashioned luck.

Is this the winning formula which will help to change pharma's bad boy rep? Ed Coke certainly thinks so: he asserts that the general public view a pharma company's corporate responsibility to society and the fairness and transparency of its governance as the most important influencers of overall reputation. In short, it is vital that CEOs lead by example, taking ownership of their company's accountability and speaking candidly about their business and research practices.

Is it possible for the industry to fix its bad rep? Well, to give a simple answer, yes. Pharma may have a mixed reputation, but it is entirely within the capability of its leading players to redress the balance.

CEO SLIP-UPS

We look at five CEOs whose controversial comments have put bad pharma in the news…

Martin Shkreli

The 33-year old former Turing CEO was dubbed '**America's most hated man'** after raising the price of Daraprim by 5,000%. His subsequent Twitter rants and smirking whilst in court on fraud charges drew the widespread condemnation and wrath of the general public and presidential candidates alike.

Jean-Jacques Bienaimé

Bienaimé's e-mail dispute with the supporters of Andrea Sloan, who were requesting that his company, BioMarin, allow her access to an investigational cancer drug, came to a head when he forwarded them an e-mail from a supposedly 'unknown' sender calling Sloan a **'spoiled, petulant brat.'**

Marijn Dekkers

Bayer's former CEO came under fire after stating that their new cancer-fighting drug, Nexavar, had been developed for **'Western patients who can afford this product,'** whilst protesting an Indian ruling which allows local suppliers to produce the drug at a fraction of the cost for the Indian market.

Jean-Pierre Garnier

Garnier became the poster boy for corporate greed after shareholders insisted that GSK's board revoke the 'golden parachute' payment of £22 million that he would receive should he ever leave the company. Garnier's response to accepting such a generous package? **"I'm not Mother Teresa."**

Michael Pearson

Pearson, whose former company Valeant was criticized for price gouging throughout his leadership, left many patients understandably put out when he attempted to defend the pricing hikes, arguing that **'my primary responsibility is to Valeant shareholders.'**

Photo sources available on request

New $350m Site To Build Pfizer's China Biosimilar Capacity

While some multinationals appear concerned about China's slowing economy and their business prospects in this market, others are forging ahead with major new investments, including Pfizer Inc., which has just unveiled plans for a large biosimilars production and R&D site.

IAN HAYDOCK ian.haydock@informa.com – 28 June 2016

Pfizer Inc.'s roughly $350m investment in a new biosimilars center in China appears aimed at tapping into China's stated policy of adding value and modernizing its biopharma sector, as well as bring on line important new global production capacity.

Shutterstock: xiao yu

The Pfizer Global Biotechnology Center, based in the Hangzhou Economic Development Area, is expected to be completed by 2018 and will create around 150 new positions. Its main function will be to produce in China to international GMP standards high quality but affordable biosimilar products, for supply to both the Chinese and global markets.

Pfizer could not comment at this stage on which specific products would be made at the site, but stressed that it was committed to bringing important therapies to patients in China.

"However, we can share that these products will be focused on addressing major health concerns in China including oncology, since cancer has been a leading cause of death in China since 2010."

Globally, Pfizer's biosimilars portfolio has been boosted by last September's acquisition of Hospira Inc., which already has a strong commercial presence in the China sterile injectables segment. Moving forward, China, including biosimilars, is seen as a major opportunity for Hospira, Pfizer has said in the past, and the new facility appears to be one concrete step towards realizing that potential.

Biosimilar products currently under development at Pfizer and that are candidates for the new China site include trastuzumab, bevacizumab, infliximab, rituximab, and adalimumab; US approval was received recently for infliximab under Pfizer's alliance with South Korea's Celltrion Inc.

MULTIPLE BENEFITS

The new Hangzhou site - the third such center globally but first in Asia for Pfizer - will also house the biosimilars and biologics quality, technical service, and logistics and engineering divisions of Pfizer China, and will carry out related process development and biosimilar clinical supply functions.

In its announcement of the investment, Pfizer emphasized how the new facility would support China's healthcare reforms, assist the Chinese government in its ongoing efforts to modernize the local biopharma industry, and promote manufacturing value and innovation.

But as well as potentially playing well politically given this alignment with broader national goals, locating the production site in China may also help to contain manufacturing costs and enable the products made there to be competitive with other major emerging manufacturers such as South Korea and India.

The facility will utilize single-use KUBio modular construction provided by GE Healthcare to increase production flexibility and reduce construction costs to 25%-50% those of equivalent standard facilities, while potentially cutting building time in half to around 18 months and also slashing emissions and energy use.

EXPANDING CHINA OPS

Pfizer already conducts some R&D activities in China and also operates several conventional production sites in the country, including in Dalian and Suzhou. The company said that in the first phase of the new biosimilars site, total production capacity would be around 25 million vials annually.

While Pfizer does not break out China sales, it reported overall growth of about 10% in this market last year, and stressed at the time it remained "very bullish" despite the slowdown.

Although there has been a series of measures to contain rising drug spending and control product costs, Pfizer's group president, Pfizer Essential Health, said in a statement on the new biosimilars facility that "We are encouraged by a series of important reforms introduced by the Chinese government that will further stimulate the industry to meet emerging health challenges, such as the incidence of non-communicable diseases and an aging population, as well as attract both domestic and foreign investment in healthcare and R&D."

In spite of the current challenges in China, several other multinationals are continuing to make significant investments there, including Novartis AG, which is building up its local R&D at a new center in Shanghai.

Germany: Companies Must Rethink Deals With Doctors

International companies operating in Germany may need to rethink how they deal with primary care physicians. For the first time, interactions with such doctors will be covered by criminal law and carrying on with certain "grey area" practices could now carry a prison sentence.

FRANCESCA BRUCE francesca.bruce@informa.com – 1 July 2016

International companies operating in Germany need to think twice about new risks associated with certain interactions with healthcare professionals, particularly primary care physicians, warns Maria Heil, a partner at the German law firm Novacos. Thanks to a new anti-corruption law that applies to the healthcare sector, some dubious but common practices, like paying too much for hospitality, will now be covered by criminal law and the penalties are much more severe.

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"It is a really important issue, we have lots of clients completely reassessing their co-operation models with primary care physicians," says Heil. "The new law changes a company's risk profile when dealing with primary care doctors and doctors working for hospitals," she adds. "It covers all kinds of interactions, including agreements, between companies and all healthcare professionals in which benefits are provided to doctors and other healthcare professionals." It means that for the first time doctors working in primary care are covered by criminal law. Until now, the criminal code applied only to corrupt agreements between businesses and employees of the state, including for example, hospital doctors or nurses. However, in Germany primary care practitioners are self-employed so were not covered by the criminal code. Instead, corrupt practices were covered by less punitive legislation like the Social Code, which codifies Germany's social security system, or the German HealthCare Advertising Act.

The law came into force in June and it is now a criminal offence, for example, to pay doctors too much for speaking at a conference or for a minimal role in non-interventional studies, to spend excessive amounts on gifts and hospitality or to rent a room at a primary care practice for advertising purposes. Heil is advising international companies with perhaps only a small team in Germany, or which distribute without using a specialized sales force, to look closely at the new law. "Most companies have agreements with primary care doctors and comply with the legal requirements, but I know lots of companies put lots of agreements in a grey zone in terms of legality. They should reassess these agreements and new risks and decide if they want to continue with them."

Penalties include fines and up to three years imprisonment. Generally, within companies, it is the member of staff who interacted with the healthcare professional that is liable. However, management can be held responsible too if they have not put in place an appropriate compliance framework.

The law comes as industry groups across Europe, in line with an initiative from the European Federation of Pharmaceutical Industries and Associations (EFPIA), are trying to improve transparency of relations between pharmaceutical companies and healthcare professionals and organizations. Industry associations like the UK's ABPI and Ireland's IPHA are publishing information on payments from companies to healthcare organizations or professionals, for example for consultancy fees or for research and development.

Obesity Companies Prolong The Inevitable As Cash Runs Out 1 July 2016

Arena and Vivus both announce efforts to conserve cash and they struggle with virtually nonexistent sales of their obesity drugs. Neither company has laid out plans for next steps.

Things continue to look dire for the companies in the obesity space and talk of a turnaround for the biotechs is not on anyone's lips as cost-cutting measures continue to be utilized.

Arena Pharmaceuticals Inc. announced after the close on June 30 that it would be trimming the fat at the already slim company, reducing its workforce by another 73% -- or 100 staffers – as it tries to conserve cash.

The company expects the cuts to be complete by Aug. 31 and to come from positions in manufacturing, research and G&A. The cuts will reduce annual expenses for personnel by $17m and operating expenses by $6m to $8m. Arena also noted that other cost cutting measures are on the way, including reductions at its Swiss manufacturing facility.

Arena will incur a cost of $6.1m related to severance and employee termination costs.

These cuts come on top of a 35% reduction in staff, about 80 employees, that was put in place last October when founder and CEO Jack Lief was unceremoniously ousted.

Amit Munshi, former CEO of floundering biotech Epirus Biopharmaceuticals Inc., took over at the beginning of June, promising a new strategic focus for the company. With his move into the top slot at the beleaguered company, Arena also terminated its chief medical officer William Shanahan on June 13.

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http://bit.ly/29h0lK6

Novartis Takes Aim At Systemic Mastocytosis With Midostaurin 1 July 2016

Novartis AG's novel anticancer midostaurin is looking promising in the rare indication of advanced systemic mastocytosis given positive data from a pivotal Phase II study just published in the New England Journal of Medicine. On the back of the results, the company said it was now working with regulatory authorities to make midostaurin (also known as PKC412) available as quickly as possible. The multi-targeted kinase inhibitor is in Phase III trials for its lead indication of acute myelogenous leukemia (AML), where Novartis hopes it will become the first step up in the standard of care for 30 years, despite some hiccups in its development along the way. The product was recently granted Breakthrough Therapy Designation in the US for adults with newly-diagnosed FLT3-mutated AML. Midostaurin also has orphan drug status in the EU and US for both AML and mastocytosis. A rare disease, advanced systemic mastocytosis is characterized by the accumulation of abnormal mast cells in the bone marrow, liver, spleen and other organs, leading to organ damage.

Goal Finally In Sight For Shire's 'Adderall Beads' Extension Strategy 30 June 2016

Shire reported positive topline results with SHP465 (triple-bead mixed amphetamine salts) in 275 adults aged 18-55 years with Attention-Deficit/Hyperactivity Disorder (ADHD), the last set of data required ahead of Class 2 Resubmission of an NDA with the US FDA by the end of 2016. The product is slated for potential US approval in the second half of 2017. SHP465 is essentially an Adderall extension strategy. "The important thing to note about this drug is that it has the same active ingredient as Adderall XR, but is designed to provide ADHD symptom control for up to 16 hours," explains Armando Uribe, analyst with Datamonitor Healthcare. A problem with Adderall is that it wears off towards the end of the day but a further early evening dose harms the sleep-wake cycle. Adderall was one of Shire's top-selling drugs until it lost patent exclusivity in 2009. If launched as planned, SHP465 will have three years of Hatch-Waxman exclusivity and at least three patents listed in the FDA Orange Book expiring as late as May 2029. Datamonitor Healthcare forecasts suggest peak SHP465 sales could reach $400m by 2025.

Mayne Cements Place On US Generics Map 28 June 2016

Mayne Pharma Group Ltd. of Australia has agreed to buy a portfolio of US generic products from Teva Pharmaceutical Industries Ltd. and Allergan PLC for $652m. The portfolio consists of 37 approved products and 5 FDA-filed products in a range of territories and indications. The two larger companies are making a series of divestments to gain antitrust approval for Teva's acquisition of Allergan's generics business for $40.5bn. Completion of the deal with Mayne will be dependent on and concurrent with the closing of the Teva/Allergan deal, which is slated to happen in the coming weeks. The acquired portfolio is expected to add more than $237m to Mayne Pharma's FY17 net sales with gross margins greater than 50%. Mayne Pharma has been working with Teva and the FTC since December 2015 and has established supply agreements with Teva for the manufacture of certain products not currently outsourced to CMOs for up to five years.

Opko Embarks On Transition To Profitability With Discount Buy 30 June 2016

While Opko Health Inc. now has multiple revenue-generating products across its diverse portfolio, the company is still struggling to be profitable and lacks the strong pipeline to be a major player in diseases with under-served patient populations. With that in mind, Opko is picking up Transition Therapeutics Inc. at a deep discount in hopes of padding its pipeline. The Miami-based company is acquiring Transition in an all-stock swap worth $60m, or $1.55 per share, that is expected to close in the second half. In exchange, Transition security holders will receive approximately 6.4m shares of Opko. The deal value is based on the five-day moving average of Opko in the days preceding the deal announcement on June 30. Opko shares were relatively flat after the announcement, trading near $9.39 apiece. Meanwhile, Transition was up 110% on the news, adding 77 cents, to trade just under $1.50 per share.

Pain's Remoxy Skips Over Panel On Rocky Road To Market 1 July 2016

Investors, for the most part, took it as a good sign the FDA told Pain Therapeutics Inc. its new drug application (NDA) for its abuse-deterrent, extended-release formulation of oral oxycodone, Remoxy, could skip being scrutinized for a second time by an advisory committee – telling the company there was no need for regulators to convene the tentatively planned Aug. 5 meeting. Shares of Pain climbed just over 9% on July 1, although closing down about 2 cents at $2.17. The firm's partner, Durect Corp., whose Oradur technology is at the heart of Remoxy's abuse-deterrent features, also benefited from the news – with its shares getting about a 5% bounce, before closing at $1.25, up 3 cents, or about 2.5%.

German Merck Identifies Pipeline Stars, Plots Course Through A Dynamic Cancer Space

As questions remain over Merck KGAA's ability to retain its top line following the patent loss for its key products Rebif and Erbitux, the German company has highlighted some of its higher priority R&D programs in its "very interesting" pipeline, as well as its strategy to make the most of the assets.

ALEX SHIMMINGS alex.shimmings@informa.com – 29 June 2016

After several years with no new product launches, Merck KGAA is expected to announce imminently the EU filing for its much-delayed multiple sclerosis treatment cladribine, and will supplement this with another submission for its key immune-oncology offering, avelumab, later this year. However, further cladribine filings including in the US will await further discussions with regulators, with the company not prepared to share any timelines yet.

Speaking to analysts on June 20, Merck's chief marketing and strategy office for healthcare, Rehan Verjee, said that over the past few years the company had successfully built up its presence in the emerging markets, particularly China, and taken back rights to the anticancer *Erbitux* (cetuximab) in Japan. "We are through the worst of the decline in the US [with the multiple sclerosis treatment *Rebif* (interferon beta-1a)]," he said. Indeed, Verjee pointed to 20 straight quarters of organic growth despite the absence of new product launches, which, he claimed, meant that the company was well poised to maximize on its new arrivals once they do debut.

Chief of these new product offerings is the anti-PD-L1 monoclonal avelumab – the plank upon which much of the pipeline rests. The upcoming filing for the product, which is subject to a 2014 joint development and licensing deal licensing deal with Pfizer, will be in second-line Merkle cell carcinoma (MCC).

Avelumab's relative importance to Merck increased further following the after the late-stage failure of evofosfamide (licensed from Threshold Pharmaceuticals) last December in advanced soft tissue sarcoma and advanced pancreatic adenocarcinoma.

This came just a few months after Merck returned to BioMarin Pharmaceutical Inc the rights to another product, *Kuvan* (sapropterin) for the rare genetic disorder PKU in the wake of its decision to exit non-core areas to focus on cancer, immunology and neurology.

Avelumab looks set to be the second PD-L1 targeted product on the market, trailing Roche/Genentech's *Tecentriq* (atezolizumab) which was approved by the FDA in May for use in bladder cancer four months ahead of schedule, as well as the pioneering PD-1 inhibitors *Opdivo* (nivolumab) and *Keytruda* (pembrolizumab).

The upcoming MCC avelumab filing will be based on the 88-patient Phase II JAVELIN Merkle 200 registration study that was recently reported at ASCO. The trial produced an objective response rate of 31.8%, with 9.1% complete responses and 22.7% partial responses. Moreover, the drug's effects were rapid, with 78.6% responding within seven weeks, and durable (83% still responding). At six months, the overall survival rate was 69% and progression-free survival was 40%.

The response rates were better when used earlier, ie with fewer prior lines of chemotherapy: the ORR was 40.4% for patients with one prior systemic treatment, and 19.4% for patients with two or more previous treatments.

Avelumab is currently in Phase III for use in second-line non-small cell lung cancer, which is progressing as planned at 70% recruitment – the first data should read out in the second half of 2017. The open-label, multicenter trial is has a primary endpoint of overall survival (OS) in patients with PD-L1+ stage IIIb/IV NSCLC that has progressed after a platinum-containing doublet chemotherapy.

Merck is pursuing this indication despite the high level of competition primarily because of its size, and the fact that molecularly-speaking this is a very fragmented disease. The idea is to get OS data in second-line disease "before the door closes in this somewhat saturated field," said Luciano Rossetti, global head of R&D, biopharma. Having OS data for NSCLC as a monotherapy is going to be very important for the company's overall combination strategy for the product.

At present Merck has nine Phase III registrational trials with single-agent avelumab, all (with the exception of MCC) very early on. These include studies in ovarian, bladder, gastric and other tumor types, plus Hodgkin's lymphoma.

But it is in new drug combinations that the next wave of cancer breakthroughs is expected, and Merck is "aggressively pursuing" studies pairing avelumab both with other IO agents, as well as other targeted therapies and chemotherapy, all the while keeping a beady eye on the competition.

But some are not so sure that avelumab will be enough to fill the void. "While the launch of avelumab will add new, organic revenues to Merck KGaA's top-line, these additional revenues are not expected to make up for the projected loss of sales from other key products, such as Rebif and Erbitux," said analysts at Datamonitor Healthcare. We currently forecast avelumab to add $1bn in sales growth through 2025, but combined sales declines for Erbitux and Rebif are projected to total just under $1.5bn in 2025 which leads to the overall decline in sales growth."

Even so, they admit there is room for upside. "It's possible that the launch of avelumab goes better than we expect it to, or that sales declines for Rebif and Erbitux will not be as severe as we currently project."

However avelumab performs if it reaches the market, it will be followed by a lull in novel product launches while the rest of the pipeline matures. The only other product currently in Phase III is a biosimilar version of adalimumab for chronic plaque psoriasis, MSB11022. Further back, the pipeline gets more interesting and Rossetti shone the spotlight on what he described as the most important high-priority programs found within it: PD-L1-TGF-beta; atacicept; the BTK inhibitor, M2951; the DNA-PK inhibitor, M3814; and tepotinib.

Click here to view Merck's clinical pipeline: http://bit.ly/29qCsD1

GW Pharma High On Epilepsy Results, Plans 2017 NDA 27 June 2016

GW Pharmaceuticals PLC is defying stigmas with strong clinical results for its cannabinoid Epidiolex in rare forms of pediatric epilepsy, announcing a second round of successful clinical trial results just three months after the first set. GW's American Depositary Receipts jumped more than 6% during June 27 trading on the NASDAQ, adding $5.18 to close at $88.49. The company announced topline results from its Phase III trial in 171 patients with Lennox-Gastaut syndrome (LGS), a rare form of epilepsy that begins in adolescence and continues into adulthood. The disease is marked by frequent seizures that often lead to head injuries and falls, as well as a high incidence of drug-resistance. The company estimates that about 30,000 children and adults have LGS in the US. Epidiolex is an oral oil derived from marijuana plants and is a pure formulation of cannabidiol, rather than tetrahydrocannabinol – the substance that induces a high.

Gilead's Epclusa Approved As First Pan-Genotypic HCV Therapy 28 June 2016

The momentum in hepatitis C continues for Gilead Sciences Inc. as its latest single-tablet, fixed-dose combination regimen, named Epclusa, obtained FDA approval June 28. The combination of the novel pan-genotypic NS5A inhibitor velpatasvir with the previously approved sofosbuvir becomes the first pan-genotypic HCV regimen approved, as well as the first single-tablet regimen for patients with genotypes 2 or 3 of the virus. Epclusa is approved for 12 weeks of therapy for patients with genotypes 1-6 of HCV, including patients with moderate or severe cirrhosis. For patients without cirrhosis or with compensated cirrhosis (Child-Pugh A), the drug does not need to be co-administered with ribavirin. For HCV-infected patients with decompensated cirrhosis (Child-Pugh B or C), dosing with ribavirin is directed. Approved under priority review, Epclusa produced sustained virologic response (SVR) rates ranging from 95% to 99% in three Phase III trials encompassing 1,558 patients with no cirrhosis or compensated cirrhosis. For the 267 Phase III patients with decompensated cirrhosis, including 87 who also received ribavirin, the drug yielded a 94% SVR rate, FDA said. Gilead announced a wholesale acquisition cost of $74,000 for a 12-week course of therapy, making it less expensive than sofosbuvir (Sovaldi), which had initial pricing of $84,000 for 12 weeks.

Biopharma/NIH 'PACT' Aims To Speed Cancer R&D 1 July 2016

A dozen biopharmaceutical companies have teamed with the National Institutes of Health (NIH) and various foundations and philanthropies to accelerate the research and development of cancer therapies – a collaborative effort that came out of discussions triggered by the White House's National Cancer Moonshot initiative. The Partnership for Accelerating Cancer Therapies (PACT) will fund precompetitive cancer research and share broadly all data generated for further R&D, with the aim of bringing more new therapies to patients in less time. NIH Director Francis Collins said the idea for the PACT, whose industry partners have yet to be revealed due to the early nature of the project, grew out of conversations he had with companies during the World Economic Forum in Davos, Switzerland this past January.

Marinus Finds Silver Lining In Ganaxolone Trial Miss

28 June 2016

After a Phase III failure less than two weeks ago, Marinus Pharmaceuticals needed a win for its lead compound ganaxolone. Unfortunately, a mid-stage study failed to meet its primary endpoint, but again, the company stayed positive. Marinus announced June 28 that ganaxolone failed to meet its primary endpoint in a 59-patient Phase II study in Fragile X syndrome (FXS). The company did not reveal the numbers behind the data, but said that despite the miss, there was a positive trend in a subgroup of patients. Further data from the study will be released at an upcoming medical meeting in July. FXS is a common genetic cause of autism and results in cognitive impairment, behavioral issues and learning disabilities. There are about 100,000 people with FXS and currently there are no approved treatments.

Correction: Arzerra in CLL

24 June 2016

Genmab has pointed out that its anti CD-20 monoclonal antibody *Arzerra* (ofatumumab) is approved for use in three settings in chronic lymphocytic leukemia in the US: frontline, relapsed and refractory, and maintenance therapy. Further, in the EU it is approved for two settings: frontline, and relapsed and refractory. In the article *Genmab Fails To Convince CHMP* in the 1 July 2016 issue, we erroneously said Arzerra was only approved for two settings in the US (frontline and maintenance), and for only one indication in the EU (frontline).

Shire Sees Future For Premature Baby Drug Despite PhII Disappointment

Shire's product candidate for a rare eye disease in premature infants has failed in a Phase II study, but secondary endpoint data suggest SHP607 might still have a future.

SUKAINA VIRJI sukaina.virji@informa.com – 30 June 2016

A Phase II study investigating the protein replacement SHP607 (previously known as Premiplex) has not met its primary endpoint of reducing the severity of retinopathy of prematurity (ROP), a rare eye condition in severely premature infants.

However, SHP607 showed positive effects related to the development of severe bronchopulmonary dysplasia (BPD), a chronic lung disease, and severe intraventricular hemorrhage (IVH), a type of brain injury, both of which were evaluated in the trial as secondary endpoints.

> 'The market opportunity for SHP607 is unchanged and [the] data appear to partially de-risk SHP607 as a prophylactic agent in premature patients'

The Phase II study included 121 extremely premature infants (born between 23 weeks and 27 weeks +6 days) randomized at birth to either SHP607 or standard neonatal care, and treated continuously until an equivalent gestational age of 30 weeks. SHP607 caused a 53% reduction in the incidence of severe BPD compared to untreated infants, and a 44% reduction in the incidence of severe IVH (Grade III and IV on centrally read ultrasounds), compared to untreated infants. There were more deaths in the treatment arm (20%) compared to untreated (12%); however, no deaths were considered related to treatment.

Another secondary endpoint, time to discharge from neonatal intensive care, was not met.

"This is the first controlled clinical trial to confirm the crucial role of IGF-1 in maturation of extremely preterm children," said Professor Neil Marlow of the University College London Hospitals, UK, and one of the clinical trial investigators. "The reduction in BPD and IVH, as the two most important morbidities suffered by these children, are welcoming and a first in neonatal medicine. It will be important to confirm these findings in additional clinical studies."

"Although the study did not meet its primary endpoint, we are extremely encouraged by the topline secondary endpoints related to lung and brain," said Philip Vickers, head of R&D at Shire. "For severe complications related to the lung and brain, there are no approved treatment options, and these data support our commitment to further investigate the potential systemic benefits of SHP607 in this population where the unmet patient need is substantial."

Shire said it now plans to begin discussions with regulatory authorities about a Phase III program of SHP607 in premature infants focusing on clinically relevant complications of prematurity.

Analysts from Bernstein are giving Shire the benefit of the doubt over the drug's potential. "This is the first test of IGF-1 in pre-term babies and the trial was 'hypothesis generating' – put the drug in and see what you can improve (one could argue that if you measure enough things, something will come up). However, it should not be too surprising IGF-1 has beneficial effects in pre-term babies and there appears to be a correlation between achieving blood level and outcomes." Leerink analysts also agree the program "remains viable."

Tesaro Doubles On Super NOVA Data, Lifts PARP Competitors

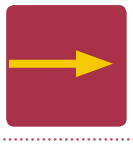
30 June 2016

Tesaro Inc.'s stock price more than doubled on June 29 after the company reported positive progression-free survival (PFS) data for its PARP inhibitor niraparib in the Phase III NOVA clinical trial, which tripled PFS for some women with ovarian cancer compared with placebo – a result that lifted the values of competing firms.

Waltham, Massachusetts-based Tesaro closed 108% higher at $77.40 per share after the company revealed its plan to submit a new drug application (NDA) to the US FDA and a marketing authorization application (MAA) to the European Medicines Agency (EMA) during the fourth quarter of 2016. Other late-stage developers of poly ADP-ribose polymerase (PARP) inhibitors, Medivation Inc. and Clovis Oncology Inc., also benefitted, ending the day with gains of 5.5% and 21.9%, respectively.

The development of PARP inhibitors has been a rocky road for the biotechnology industry. The mechanism was dismissed as ineffective in broader patient populations, but then drug makers found that PARP's role in DNA repair and BRCA-positive tumor cell growth justified development in certain populations.

That's why Tesaro's Phase III NOVA trial relied heavily on identification of patients as germline BRCA mutation (gBRCAmut) carriers; non-germline BRCA mutation carriers (non-gBRCAmut), who had homologous recombination deficient (HRD) tumors, according to the Myriad Genetics Inc. myChoice HRD test; and a broader group of non-gBRCAmut carriers. Niraparib significantly improved survival in all three groups. mandy.jackson@informausa.com



Click here to view Merck's clinical pipeline: **http://bit.ly/29kGJ8P**

FDA's Pazdur: I Won't Turn Into A Bureaucrat; My Presence Will Be Felt

DONNA YOUNG donna.young@informa.com – 30 June 2016

Shutterstock: Tomas Urbelionis

Richard Pazdur, who is moving from being the head of the FDA's Office of Hematology and Oncology Products (OHOP) to the agency's acting director of the newly created Oncology Center of Excellence, established under the White House's National Cancer Moonshot initiative, sat down with reporters on June 29 to explain his new role, but warned don't think he's just going to turn into some sort of a bureaucrat and to anticipate his presence to continue to very much be felt at OHOP.

Richard Pazdur, who was named the acting director of the FDA's new Oncology Center of Excellence (OCE), which is being created at the agency as part of the White House's National Cancer Moonshot initiative, said don't expect him to just turn into some sort of a bureaucrat in his new job or that he'll no longer be hanging around the Office of Hematology and Oncology Products (OHOP), which he's led since it was established more than a decade ago.

"My presence will be felt" at OHOP, Pazdur told *Scrip* and a handful of other reporters at vice president Joe Biden's June 29 moonshot summit at Howard University in Washington, where the new OCE chief's role was officially announced.

Pazdur emphasized that he didn't want his transition to the new center, which the FDA is describing as a "program" where the combined skills of regulatory scientists and reviewers with oncology clinical expertise in drugs, biologics and devices will come together to support an integrated approach to the advancement of cancer treatment, to be a disruptive process.

"There have been agreements with companies and evaluation of drugs and certain principles I've established" at OHOP, he said.

"I really enjoy what I do, so it's not like I just want to move to become a bureaucrat or administrator," Pazdur declared.

In his new job at OCE, Pazdur said he anticipated "working with the same group of people" he's been interacting with for many years at OHOP, whom he referred to as "personal friends and professional acquaintances."

"So it's not that I'm going to be stepping away in a sense," Pazdur explained. "I am going to be there. Believe me, I will be there."

In fact, he said he likely will continue "running" and attending OHOP's Monday and Friday group meetings, where oncology regulators go over product applications under review.Pazdur said his yet-to-be-named replacement at OHOP – an office he's brought from 12 medical oncologists to 70 during his tenure – "will not be the same role as I have now, obviously, because I am there and the center is there."

So that person won't be completely filling Pazdur's shoes at OHOP. But he said he's excited to take on the challenge of setting up the OCE because it's "uncharted territory."

"I always like to do things that are unique and new," Pazdur said. "When I came to FDA in 1999, I had a vision for what oncology should be and that was a more interactive agency and a really academic focus. And this is really keeping in line with this and an expansion of a vision I had in 1999."

He emphasized the OCE currently is evolving and in fact, he is taking on the role of acting director to establish its structure and determine its direction, although Pazdur said he's not simply been given carte blanche.

"Obviously, I'm responsible to other people," Pazdur said, noting he now will be reporting directly to FDA commissioner Robert Califf rather than to Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), where OHOP is housed.

Woodcock and the directors of the FDA's Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH) will also have opportunities to weigh in on OCE's path forward, he said. Pazdur said he's not under any specific deadline to set up the OCE.

"What I'm more interested in doing is making sure everybody's voice is heard," he said. "One of the first things I want to do at this point is to sit down with the review staff."

Pazdur said the number of employees who will make up the OCE will depend on its structure and budgeting. President Barack Obama requested $75m in his fiscal year 2017 budget for OCE – dollars that must still be approved by Congress – but Pazdur said the FDA has the necessary funds to get the program off the ground, although he noted it has yet to be defined how much will be "borrowed" from the agency's drug, biologics and device centers to set it up.

While there's currently communication among OHOP reviewers and those at CBER and CDRH when examining applications for combination products, Pazdur said the OCE aims to ensure there's a better understanding among the agency's scientists of each of the centers' respective regulatory processes.

While the idea to set up the OCE was a patient-driven concept, Pazdur noted the FDA has been seeking input from numerous stakeholders, including industry, at various listening sessions over the past few months – pointing out that communicating with people outside the agency has been key. But Pazdur said he expects there to be some uneasiness in moving the new program forward.

'Moonshot' Pilot Aims To Fast Track Cancer Immunotherapy Patents

The Obama administration is offering biopharmaceutical companies and other inventors of cancer immunotherapies the opportunity to get their patent applications examined within 12 months under a special accelerated pilot program as part of the White House's $1bn National Cancer Moonshot initiative.

DONNA YOUNG donna.young@informa.com – 29 June 2016

Biopharmaceutical companies and others pursuing cancer immunotherapies may be able to get their US patent applications reviewed faster than usual under a new pilot program being instituted as part of the White House's $1bn National Cancer Moonshot initiative – an effort to achieve a decade's worth of advances in cancer prevention, diagnosis, treatment and care in the next five years.

The fees to obtain the special status for the accelerated patent examination are being waived under the pilot

With about 900 applications received annually from around the world in the cancer immunotherapy space alone, the pilot program aims to catalyze innovative new treatments – from conception through regulatory approval – so those medicines can reach patients faster, the US Patent and Trademark Office (US PTO) said.

The agency unveiled the program in a June 28 Federal Register notice – a day ahead of an all-day summit being convened by the White House at Howard University in Washington, where hundreds of representatives from industry, government, academia, patient advocacy groups and other stakeholders are gathering to participate in workshops, discussions and other events focused on how to advance the moonshot effort, which is being led by Vice President Joe Biden

The immunotherapy patent pilot is just one of several government and private-sector measures being launched to coincide with the June 29 moonshot summit, which Biden will host, with the help of American actress and comedian Carol Burnett – both of whom have lost children to cancer.

Under the US PTO's program, the agency said it would prioritize applications containing claims to methods of treating cancer using immunotherapy for those who request the special status and meet the requirements, with an objective of completing the reviews within 12 months.

The fast tracking will be open to any applicant, including early-stage biotechnology companies, universities and large pharmaceutical firms, the US PTO said. It said entities with products already in FDA-approved clinical trials also would be able to opt into the acceleration program.

All petitions seeking the special status under the cancer immunotherapy pilot program must be filed by June 29, 2017, the US PTO said.

The fees to obtain the special status for the accelerated patent examination are being waived under the pilot, the agency pointed out.

The pilot is planned to be a one-year program, but the US PTO said it could decide to extend it, although it also said it could terminate the project, depending on the workload and resources needed to run it, public feedback and a determination of its effectiveness.

To be eligible for the cancer immunotherapy pilot program, patent applications must be in the field of oncology and contain at least one claim encompassing a method of ameliorating, treating or preventing a malignancy in humans wherein the steps of the method assist or boost the immune system in eradicating cancerous cells, the US PTO explained.

Litigation Aside Biosimilar Avastin Just Got Cheaper In India

27 June 2016

Another biosimilar version of Roche's anticancer, *Avastin* (bevacizumab) has just arrived on the Indian market despite the shadow of ongoing litigation. The launch, cheered by some activists, takes prices of biosimilar bevacizumab lower, amid allegations that Roche has been pursuing "vexatious" litigation against Indian competitors.

The Hyderabad-based Hetero group, on June 27, announced the launch of its biosimilar bevacizumab (marketed as *Cizumab*) for the treatment of metastatic colorectal cancer (mCRC).

Cizumab is available as a single dose vial in two strengths - 100mg and 400mg - and has been priced cheaper than competitor Reliance Life Sciences' recently launched biosimilar bevacizumab version, though it's unclear if discounts will bridge the pricing gap. Cizumab 400mg, it is learnt, comes at INR102,600 ($1,509) as against INR105,010 for the same strength of Reliance's BevaciRel and the reported price of about INR108,000 for Avastin.

Actual prices to patients may work out to be much lower given the discounts given in trade, though no official word on this was immediately available.

Cizumab will be marketed and distributed by group firm, Hetero Healthcare Limited, though it's not immediately clear if Hetero too will rope in co-marketing partners as has Reliance. Bevacizumab, which is the Hetero group's third biologic after darbepoetin alfa and rituximab, will be manufactured at the company's dedicated facility in Hyderabad, Hetero said.

More competition appears to be on the horizon after a subject expert committee (SEC), which advises the Indian regulator on trial-related permissions recommended for marketing authorization bevacizumab versions of Intas Pharmaceuticals Ltd.

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Esperion Says FDA Stance Means No Clear Regulatory Path For ETC-1002 29 June 2016

Esperion Therapeutics Inc. had been working with the FDA in an attempt to forge a new regulatory path for its cholesterol drug ETC-1002 in statin-intolerant patients, a population the US agency has been very cautious about in the past. The Ann Arbor, Michigan-based group had proposed a plan to conduct a Phase III study using LDL-C lowering as a surrogate, but still approvable, efficacy endpoint in statin-intolerant patients. But Esperion on June 28 announced that the FDA had now rejected the idea. Esperion said it therefore now planned to submit a New Drug Application to the agency for a CV disease risk reduction indication on the basis of a successful completion of a cardiovascular outcomes trial dubbed CLEAR, set to start in the fourth quarter of 2016, and include results of the LDL-C lowering efficacy studies, by 2022. ETC-1002 (bempedoic acid) inhibits ATP citrate lyase, an enzyme on the cholesterol biosynthesis pathway. It works similarly to statins in that it up-regulates LDL receptors, so it has a trusted mechanism of action, but unlike statins it achieves the LDL-C lowering without the muscle pain side effects, according to the company.

Brexit Talks Must Prioritize Patient Access, Avoid Regulatory Divergence, Says EFPIA 30 June 2016

Patient access to new drugs must be a priority in the negotiations over the UK's exit from the EU, as must the need to ensure that the UK and EU drug regulatory systems don't diverge, says the European industry federation, EFPIA, one week after the momentous vote. The European pharmaceutical industry federation EFPIA says that the interests of the patient and access to medicines must remain at the centre of any decisions taken in the context of negotiations over the UK's exit from the EU, and that the UK and EU drug regulatory systems must not be allowed to diverge. It has also expressed concern over the cloud of uncertainty now gathering over investment decisions and business planning. One week after 52% of UK voters unexpectedly plumped for a "Brexit", EFPIA said that said policymakers would need to ensure that rapid access to innovative medicines across Europe, including the UK, were at the heart of healthcare policy. The current "exciting new wave of pharmaceutical innovation" would play a key role in addressing the challenges faced by patients and healthcare systems in Europe, it noted. "Ensuring that Brexit does not negatively impact the regulatory capacity, processes and time-frames for the introduction of new medicines must be a priority, including regulatory integration of the UK's medicine agency into the EMA [European Medicines Agency]'s ecosystem," the federation said in a statement. Asked what this meant exactly, a spokesman said it was important to ensure that the regulatory systems did not diverge, and that it would be "unhelpful to have separate UK and EU systems." The decisions to ensure this does not happen "will remain in the hands of the EU (Commission) and the UK government," it added. It is, of course, difficult to pin down what direction the regulatory systems will take until we have some idea of the likely future arrangements between the UK and the EU. The EFPIA spokesman said it was "impossible to speculate what would happen at this stage as we do not know which model will be selected by the UK and how the negotiations with the EU will progress."

ABPI Unveils UK's Disclosure Site For Payments to Health Professionals 1 July 2016

Disclosure UK, a new database requiring pharma companies to declare payments made to healthcare professionals, will record any payments made by companies to UK healthcare professionals for attending continuing professional development events, associated travel and hospitality costs, and any payments for work as advisers or consultants to companies. UK-based drug makers and others within Europe are now publicly disclosing payments that they made to healthcare professionals last year as part of an industry-wide move to promote transparency that will allow the public to find out whether their doctor receives payments from pharma groups. The Association of the British Pharmaceutical Industry (ABPI) unveiled a central online platform for payment disclosure on June 30. It's part of the European Federation of Pharmaceutical Industries and Association's (EFPIA's) new disclosure code on the "transfer of value" to healthcare professionals and healthcare organizations, under which companies will publish on their own website or on another public platform all such payments including consultancy fees for speaking, and travel or registration fees for attending medical congresses. Besides the the UK, Belgium, Ireland, Portugal, Russia, the Netherlands and the Czech Republic have also launched central online platforms for disclosure under the EFPIA disclosure code, which is being applied in 33 countries. Pharma payments for R&D and clinical trials activities by healthcare professionals will however only be disclosed by each company in aggregate; investigators working on industry-sponsored trials will be listed in EMA's clinical study reports.

Fauci: Borrowed Cash Won't Carry Zika Efficacy Trials

DONNA YOUNG donna.young@informa.com – 2 July 2016

Cash borrowed from various US government programs, including the Ebola response, is enough to get at least two Phase I Zika vaccine trials underway, but those funds won't carry the efficacy studies – the preparations of which must get off the ground next month. So Congress needs to allocate new dollars within the next few weeks or the Phase II trials will be in jeopardy, Anthony Fauci, the nation's top infectious disease official, told Scrip.

While the US National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, has enough funds – albeit borrowed from other programs – to start a Phase I trial of an experimental Zika virus vaccine next month and even bring it to fruition, if Congress fails to allot new dollars within the next few weeks, a Phase IIb study may never get off the ground, or at least, be significantly delayed, the agency's chief said.

Anthony Fauci, director of the NIAID, told *Scrip* the agency expects to now initiate the Phase I study testing the safety and immune response in 80 healthy volunteers of an investigational DNA-based vaccine, which uses a strategy similar to what was employed for an experimental product developed to prevent the West Nile virus, which is a flavivirus like Zika, in mid-to-late August – a timeline that's been moved up a few weeks.

But the government had to pull dollars away from other programs, including Ebola, to get things moving with Zika, a virus that has minimal effects for most people, but has devastating consequences if pregnant women contract the disease, which can cause their fetuses to develop microcephaly, a rare neonatal malformation in which a baby's head is much smaller than normal, resulting in developmental and other disabilities.

Now, Fauci is waiting on Congress to allocate new funds – specifically, the $1.9bn requested in February by President Barack Obama, who on July 1 again blasted lawmakers for their "politics as usual, rather than responding smartly to a very serious public health request."

"That request has been up there for quite some time and has gotten caught up in politics, and we've seen people trying to attach legislation on a bunch of unrelated topics to this funding," Obama scolded from the White House Oval Office, where he had just been updated by Fauci, Centers for Disease Control and Prevention Director Tom Frieden and Health and Human Services Secretary Sylvia Mathews Burwell on the status of the US Zika efforts.

Obama insisted that until the Zika funding bill gets done, lawmakers should not adjourn for their summer recess, in which the House departs on July 15 and does not return until Sept. 6, while the Senate closes up shop on July 18 and stays away until Sept. 5.

House and Senate Republicans settled on a $1.1bn package – $800m less than Obama is seeking – which Democrats are objecting to because it would cut about $750m from various healthcare budgets, including Ebola, and would place certain limitations on birth control services for women in the US and Puerto Rico.

House Republicans on June 23 pushed the measure through in a middle-of-the-night vote, which was mostly along party lines, but the bill has been stalled in the Senate after it failed to garner the 60 votes needed to close debate. "We have a chance at developing a vaccine quickly that will help a lot of people as long as Congress, over the next few weeks, does its job," Obama demanded.

In an interview, Fauci explained that even though the NIAID is not expected to start its first Phase IIb trial testing the efficacy of the DNA-based Zika vaccine until January, he needs funds within the next few weeks so that he can start preparing the study sites – activities he emphasized must be done months ahead of time.

"So even though up to now nothing has slowed down, if we don't get the money the president has asked for quite soon, within the next few weeks, all of a sudden we are going to find ourselves in August without enough money to be going ahead to preparing the sites for the Phase II," he lamented.

Fauci noted that recent results of studies testing the DNA-based vaccine and a whole-particle inactivated vaccine in mice showed both products were protective and that "there's no doubt that you can induce a good immune response."

He said both of those candidates will be moving "very soon" into non-human primate studies.

"And I'm certain that we're going to find the same results in non-human primates that the vaccine induces quite a good response," Fauci declared.

So for the early testing, "everything seems to be on schedule, if not even a little ahead of schedule," he said, noting that a second Phase I study is planned for later in the fall – that one testing the whole-particle inactivated vaccine.

Both Phase I trials will be conducted in the Washington area and at yet-to-be disclosed NIAID-funded sites, Fauci said.

But, he said, for the Phase II trials, "the president made a pretty strong statement that we really need to get this funding, and directly addressed Congress saying, 'Let's go, we need to move here'" or the studies will be in peril.

COMPANY PARTNERING

The NIAID also is pursuing three other approaches for Zika: a live-attenuated chimera product that builds on a similar vaccine approach for the closely-related dengue virus; a genetically engineered version of the vesicular stomatitis virus; and an mRNA-based-vaccine.

The agency is partnering with Brazil's Instituto Butantan, which is the largest producer of immunobiologicals and biopharmaceuticals in Latin America, on the live-attenuated Zika chimera product, although it's likely not going into a trial in humans until 2017, Fauci said.

From the start, there was considerable interest from biopharmaceutical companies in pursuing a vaccine against Zika, with Sanofi, NewLink Genetics Corp. and Inovio Pharmaceuticals Inc. among those in the lead in chasing a product.

Fauci said "two major pharmaceutical companies are already in active discussions of formalizing partnerships with us" – the identities of which the NIAID may soon be ready to reveal.

But without the federal dollars to fully support the NIAID's activities, Fauci has worried companies would back away – leaving the government to carry the burden on its own, like it did with a West Nile virus vaccine, which never made it to the market.

Five Principles For Building Successful Digital Partnerships

In the first of a new series of exclusive columns from senior thought leaders at Deloitte, Roland Foxcroft shares his view on how to build partnerships with digital leaders to create mobile apps that satisfy all stakeholders.

ROLAND FOXCROFT – 4 July 2016

Investment in digital health is growing rapidly and has cumulatively reached $15.5bn in the US alone. However, much of this growth has been characterized by fragmentation for pharmaceutical companies. Despite iOS and Android hosting over 165,000 health apps, more than 48% of pharmaceutical company published apps do not have a single user review. It is little wonder, therefore, that a recent study has highlighted that only 13% of pharmaceutical leaders are satisfied with their current digital activities.

Currently, 82% of mobile apps have just one or two functions which only allow them to support one specific part of the pharmaceutical value chain. However, digital technology, when properly deployed, allows us to reuse both data and functionality. Our most digitally mature clients have moved away from building individual mobile and internet solutions with just one or two functions. Instead, they are beginning to link these solutions to create integrated platforms that can be used by different teams throughout the business. For example, the same technology could be used by development teams to digitally enable a clinical trial and then re-used by commercial teams to support product launches subject to adaptive licencing.

As pharmaceutical companies begin to focus increasingly on linking digital solutions, we are seeing a move away from investing in recreating existing technologies. New forms of partnership between pharma, digital companies and the healthcare system now allow digital leaders to access the very best individual digital solutions where appropriate.

We have identified five principles to help leaders develop these partnerships:

1. Due diligence beyond technology. During the initial partner selection phase, companies often bias their assessment toward a holistic procurement process for technology today, rather than thinking about a partner of the future. A strategic partner should have the ability to balance short term technology delivery with longer term partnership development. Successful alliances are formed by those companies with a broader view of partners' priorities, leadership skills and cultural compatibility.

Shutterstock: ra2studio

2. Strong governance that shares both benefits and risks. Companies often do not invest enough time and resources into developing a governance framework that clearly defines roles and responsibilities beyond immediate delivery plans. This often leads to unresolved cross-organizational tension. Strong alliance frameworks fairly allocate the risks and benefits; reinforce incentives; and provide a collaborative forum for partners to openly address emerging issues.

3. A pan-partner view of compliance. Digital alliances raise complex challenges around pharmacovigilance, ethics, information governance and other regulatory issues and are complicated further due to risk processes that vary across organizations, with many prospective digital partners demonstrating inexperience in the healthcare sector. Early development of pan-partner compliance processes is critical to align expectations, avoid unexpected delays, and reduce risk.

4. A networked view of stakeholder engagement. Too often, digital partnerships underemphasize the level of interaction with enabling and blocking stakeholders, largely as a result of placing too much focus on end customers, like physicians or patients. Nevertheless, many delays arise from other stakeholder groups, such as government policy-setting bodies, public health authorities, doctors' unions, and patient advocacy charities. An insider view of the local healthcare system is often essential to avoid costly missteps.

5. Management of value, not insight. In the rush to deliver insights straightaway, partners often deprioritize planning future implementation programs. Successful programs articulate how they link to each partner's corporate strategy early on and then proactively identify which organizational processes should be modified and what new skills will need to be developed in order for the partnership to reach its full potential. As good digital initiatives deliver benefits to multiple functions in each partner's organization, managing this change is often more complex

To make these partnerships successful, digital leaders need new skills in their team – strategy, external relationship management and governance, risk management, communications and change management. In many cases, these skills are not accessible in digital teams as they are currently configured and so digital leaders will need to either reshape their teams or else access talent from elsewhere in the enterprise.

Don't Fear The Pricing Reaper

ANDY SMITH – 4 July 2016

The drug pricing debate has tarred many brushes in the pharmaceutical value chain. Whilst politicians may not yet be able to distinguish between the brazen price inflation of generic drugs and the high prices of innovative and recently launched branded drugs, the debate and rhetoric will eventually polarize. That polarization may be helped by new drugs with potentially very high list prices that are destined to be prescribed to very few patients.

Towards the end of June the specialty pharmaceuticals company Impax Laboratories Inc. announced the $586m acquisition of a portfolio of 15 generic products that was, in part, meant to satisfy the competition authorities and enable the acquisition of the generics business of Allergan PLC by Teva Pharmaceutical Industries Ltd. About a year ago, such an accretive acquisition of difficult to manufacture and limited competition alternative dosing form generic drugs – which the analysts from Cowen suggested were acquired for a "reasonable price" – might be met with a positive share price movement for the acquirer. Instead, the share price of Impax finished the day the acquisition was announced down over 10%. Since the acquisition would be paid for by an increase in Impax's debt, it might have been logical to expect some share price weakness as the debt holders sold short the stock in order to hedge their exposure to Impax's specific risks. However, I was bemused by the extent of the sell-off. The analysts from JP Morgan clarified this issue when they subtracted the expected faster-growing newly-acquired product sales from Impax's revised 2016 sales guidance. This implied a slowing of the original stand-alone Impax business, probably as a result of generic drug price deflation. As recently as the end of February, Impax's financial results included significant sales and earnings beats of analysts' consensus estimates. While its 2016 earnings guidance was below consensus, sales growth was still implied for the year. Up until that point, I almost believed the commentary of bigger generics companies like Mylan NV and Teva at their first-quarter earnings announcements when they implied that they were too big to be affected by generic pricing pressures. However after the experience of Impax it seems better to assume that generic pharmaceutical companies may only be able to deflect pricing pressures by their scale and associated efficiencies for a time. To paraphrase John Maynard Keynes, in the long run generic price deflation will come to all. It was just ironic that in attempting to address this inevitability by acquiring products with growth, Impax's growth prospects for its stand-alone business were exposed.

If there is now no hiding place from generic price deflation and the only answer is to acquire or develop new products with sales growth then innovative companies should be favored. Try telling that to the holders of Gilead Sciences Inc. whose $84,000 per course price for its HCV antiviral *Sovaldi* (sofosbuvir) started the drug pricing debate long before US senators worried about the generic pricing practices of Turing Pharmaceuticals AG and Valeant Pharmaceuticals International Inc. Gilead's price to earnings (PE) ratio is now down to 7.2 which implies the sort of (low) growth investors would associate with the regulated utilities sector, rather than the free-pricing biotechnology sector.

A discussion last month with the CFO of gene therapy company Spark Therapeutics Inc. suggested an (albeit retrospective) answer to Gilead's valuation conundrum. Gene therapy companies like uniQure NV and bluebird bio Inc. based their US IPOs on prices for single treatment courses in the millions of dollars. That sort of sticker shock has largely been superseded by the thinking of companies like Spark which are leaning towards performance-based or annuity pricing in discussions with payers. Indeed, the realization by investors that the $1m dose is untenable, added to the efficacy failure of the products of uniQure and bluebird, has resulted in their share prices falling by more than 70% in the last year. Similarly the Gilead approach to innovative drug pricing that starts at a point the market will bear is now about as last century as licking a stamp. Imagine what would have happened if Gilead had gone to private health insurers and government payers with two alternative pricing approaches for Sovaldi in 2013. The choice of either $84,000 up front, or something like $10,000 a year for as long as the patient remained cured of HCV (bearing in mind the long-term efficacy of Sovaldi-based regimens was unknown prior to its launch) would have probably resulted in most votes for the annuity approach with its initial lower, predictable and smoothed cash flows. At least two barriers exist to this approach. Firstly Gilead probably and correctly assumed that its investors would favour the first up-front approach and would incorporate a much lower multiple into their valuations of the company if they had annuity pricing. On the other hand, with a PE ratio of only 7.2, that is where they find themselves today without the security of the long-term cash flows of annuity pricing. Secondly, as the soon-to-be ex-Prime Minister of the UK realized on the morning of the Brexit vote, it is a lot harder job negotiating and shepherding a country though uncharted waters than it is managing business as usual. Thus the supporting market access and reimbursement dossiers for the first blockbuster pharmaceutical or biotechnology product that incorporates annuity pricing will have to be radically different and much harder work than those in the past.

It now appears that a lower global interest rate environment is one of the consequences of the UK vote to leave the EU. In that environment, companies that can generate growth will be highly prized. Investors, company management, health economists and politicians will have to realize that business as usual is not the answer if that prize of long-term growth is to be achieved. Faint hearts never won fair maidens.

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager's view on life science companies. He has been lead fund manager for four life science–specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

CLICK
Visit scrip intelligence.com for the entire pipeline with added commentary.

Late-stage clinical developments for the week 17–23 June 2016

LEAD COMPANY	PARTNER COMPANY	DRUG	INDICATION	MARKET
REGULATORY APPROVAL				
Opko Health Inc.	–	Rayaldee (calcifediol)	secondary hyperparathyroidism	US
Gilead Sciences Inc.	–	Odefsey (emtricitabine, rilpivirine and tenofovir alafenamide)	HIV	EU
Medical Developments International Ltd.	Mundipharma International Corp. Ltd.	Penthrox (methoxyflurane)	moderate to severe pain	France
Japan Tobacco Inc.	Torii Pharmaceutical Co. Ltd., Gilead Sciences	Genvoya (elvitegravir, cobicistat, tenofovir alafenamide)	HIV	Japan
Sanofi Pasteur	–	Dengvaxia (dengue vaccine)	dengue fever	Costa Rica
SUPPLEMENTAL REGULATORY APPROVAL				
Eli Lilly & Co.	–	*Cyramza* (ramucirumab)	non-small cell lung cancer	Japan
Allergan Inc.	AstraZeneca PLC	*Avycaz* (ceftazidime and avibactam)	intra-abdominal infections	US
REGULATORY FILING ACCEPTED				
Santhera Pharmaceuticals	–	*Raxone* (idebenone)	Duchenne muscular dystrophy	EU
ORPHAN DRUG DESIGNATION				
GW Pharmaceuticals PLC	–	*Epidiolex* (cannabidiol)	infantile spasms (West syndrome)	US
Wave Life Sciences Pte. Ltd.	–	WVE-120101	Huntington's disease	US
Anavex Life Sciences Corp.	–	ANAVEX-2-73	Infantile spasms (West syndrome)	US
Nippon Shinyaku Co. Ltd.	Actelion Pharmaceuticals Ltd.	*Uptravi* (selexipag)	chronic thromboembolic pulmonary hypertension	Japan
FAST-TRACK STATUS				
Fate Therapeutics Inc.	–	ProTmune	graft-versus-host disease	US
Oncternal Therapeutics Inc.	–	TK216	Ewing sarcoma	US
BREAKTHROUGH THERAPY DESIGNATION				
Incyte Corp.	Eli Lilly & Co.	*Jakafi* (ruxolitinib)	graft-versus-host disease	US
CHMP NEGATIVE OPINION				
Novartis AG	Genmab AS	*Arzerra* (ofatumumab)	maintenance therapy for relapsed CLL	EU
REGULATORY FILING				
Mitsubishi Tanabe Pharma	–	*Radicut* (edaravone)	amyotrophic lateral sclerosis	US
ROLLING NDA FILING INITIATED				
Ariad Pharmaceuticals Inc.	–	brigatinib	non-small cell lung cancer	US
PRIORITY REVIEW				
Nicox SA	–	AC-170 (cetirizine eye drops)	ocular itching due to allergic conjunctivitis	US
REMS APPROVAL				
H. Lundbeck AS	–	*Sabril* (vigabatrin)	epilepsy	US
PRODUCT LAUNCH				
Braeburn Pharmaceuticals	Titan Pharmaceuticals Inc.	*Probuphine* (buprenorphine)	drug addiction	US
Collegium Pharmaceutical	–	*Xtampza ER* (oxycodone)	chronic pain	US
Clinuvel Pharmaceuticals	–	*Scenesse* (afamelanotide)	porphyria	Netherlands
Shionogi & Co. Ltd.	AstraZeneca PLC	*Crestor OD* (rosuvastatin)	hypercholesterolemia	Japan

Source: Sagient Research's BioMedTracker

Acorda Therapeutics Inc., a company focused on neurological disorders, has appointed ***Burkhard Blank*** chief medical officer (CMO) – effective immediately. Blank was appointed as the company's interim CMO in January 2016 and has previous experience of serving as CMO for various biopharmaceutical companies including Boehringer Ingelheim. Blank has also been a strategic advisor to several biotechnology companies.

Takeda Pharmaceuticals International AG. has appointed ***Antonio Palumbo*** to the newly created role of distinguished research fellow oncology. Palumbo carries more than 26 years' experience in hematology/oncology cancer research and previously was director, myeloma unit department haematology, University of Torino, Italy. He is currently a member of the Italian Society of Haematology, European Society for Medical Oncology, American Society of Haematology, and the American Society of Clinical Oncology.

Anti-infectives company, **Auspherix**, has appointed ***Professor William Hope*** to its scientific advisory board (SAB). Hope is a NIHR clinical scientist and professor of therapeutics and infectious diseases at the University of Liverpool, UK and was recently named chair in the department of molecular and clinical pharmacology at the university. Previously, he was chair in therapeutics and infectious diseases at the University of Manchester.

Clincal-stage specialty biopharma **DBV Technologies** has appointed ***Lucia Septién*** chief medical officer. Septién brings more than 20 years' of experience in the pharma industry and has held various senior positions, leading R&D and portfolio management strategy teams. Prior to DBV, Septién was vice president, global neurosciences, responsible for the medical strategy of the Botulinum Toxin portfolio at Ipsen. Septién spent majority of her career at Pfizer, where she was vice president of the specialty care business unit, Europe and prior to this at Wyeth Pharma, where she was assistant vice president, global neuroscience.

Curetis, a company focused on developing next-level molecular diagnostic solutions, has appointed ***Christopher M. Bernard*** president and CEO of its North American subsidiary Curetis USA Inc. – effective immediately. Bernard brings over 22 years' experience to the company and previously was chief commercial officer of Epic Sciences. Prior to this, he was officer and senior vice president, sales and marketing at Metabolon Inc., and before this he served as officer and vice president, sales and marketing of Abaxis Inc.

Umercine Cognition AB., a company focused on treatment for hepatic encephalopathy in patients with liver disease, has appointed ***Bruce Scharschmidt*** member of Umecrine's board of directors and senior development advisor. Most recently, Scharschmidt was senior vice president and chief medical and development officer at Hyperion Therapeutics (acquired by Horizon Pharma Inc. in 2015). He has held senior positions at Novartis, Chiron and the University of California, San Francisco, where he was professor of medicine and chief of gastroenterology.

Oncology focused **Ignyta Inc.** has appointed ***Christian V. Kuhlen*** to serve as its general counsel and secretary, replacing Matt Onaitis. Kuhlen was general counsel, vice president and secretary of Genoptix Inc., since 2007 and continued to serve in these roles once it was acquired by Novartis in 2011. Prior to Genoptix, Kuhlen was an attorney in private practice with Cooley LLP.

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