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Pfizer v. J&J Sets Stage For Biosimilar Showdown Over Exclusive Contracts

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A lawsuit filed by **Pfizer Inc.** against **Johnson & Johnson** over its defensive contracting for *Remicade* (infliximab) will be a significant commercial test for the US biosimilar market. The complaint could have implications for how far brand manufacturers can go when it comes to protecting their blockbuster franchises through payer contracts, and whether or not biosimilars will have the chance to make substantial inroads in competitive markets.

Pfizer announced Sept. 20 that it filed suit against J&J in the US District Court of Eastern Pennsylvania over what it calls anticompetitive practices that have denied patients access to its own version of infliximab, *Inflectra*, and undermined price competition in the emerging biosimilar market. J&J's exclusive contracting methods have effectively blocked Inflectra from accessing 70% of the commercial market, the lawsuit claims, even as Pfizer has offered to guarantee insurers it will offer Inflectra at a lower price versus Remicade.

> "As of September 1, 2017, about 90% of healthcare provider accounts using infliximab had not purchased any Inflectra, Pfizer says.

The case could be groundbreaking in that Inflectra is a test for how the US biosimilar market might unfold in the near-term. The biosimilar, developed by **Celltrion Inc.**, is the first copycat version of a widely used and expensive monoclonal antibody to launch in the US. Pfizer launched Inflectra in the US in November 2016. *(Also see "Pfizer Will Support Inflectra Launch With Dedicated Sales Force" - Scrip, 14 Nov, 2016.)* Yet, despite payer enthusiasm for biosimilars that could lower the cost of popular biologics, Pfizer has struggled to secure reimbursement for Inflectra from commercial payers.

The issue, as Pfizer previously outlined in its second quarter earnings call, is that J&J has been able to monopolize the market through exclusive contracting, offering both steep discounts and bundling other portfolio products into contract negotiations. *(Also see "Exclusive Remicade Contracts Are Slowing Biosimilar Uptake" - Scrip, 1 Aug, 2017.)* Indeed, J&J hasn't been keeping its initiatives under wraps and has been talking about the moderate impact of the Inflectra launch on Remicade thus far. *(Also see "Remicade: Biosimilars And Pricing Pressure Wear On J&J's Blockbuster*

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A monthly-updated listing of recommendations from the European Medicines Agency's Committee for Medicinal Products for Human Use on the authorization of new medicines in the European Union, and updates on EU marketing authorization changes recommended by the CHMP.

Problems With Alternative Levothyroxine In France Force Merck To Switch Back To Original

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French patients who have experienced adverse reactions to a new formulation of Merck KGaA's hyperthyroidism drug Levothyrox are to be given temporary access to the original formulation, pending the availability of other brands of levothyroxine. Merck says the vast majority of patients have had no problems with the new version.

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inside:

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Brand" - Scrip, 18 Jul, 2017.)

As Pfizer points out in the lawsuit, the risk is that J&J's strategy could have long-lasting impact. J&J's "biosimilar readiness plan" – as J&J calls it – is poised to "become the playbook for biologic originator firms seeking to preserve their dominance in the face of biosimilar competition," Pfizer says.

J&J rejected the allegations, however. In an email, Janssen Biotech President Scott White said, "We are effectively competing on value and price and to date, Pfizer has failed to demonstrate sufficient value to patients, providers, payers and employers."

"Competition is bringing down the overall cost of infliximab, including Remicade, and will continue to bring down costs in the future," he added.

It is true the insurer is still getting the discount either way, but the larger question is what this kind of aggressive contracting could mean for the long-term viability of the biosimilar market and what role insurers should play in fostering the market at this early stage. It's also not clear what would happen if insurers refused to accept the exclusive contracts – would J&J really hold back on millions of dollars in rebates and discounts at a time when the pharmaceutical industry is facing growing public backlash over high drug prices, and the industry's reputation appears increasingly in question?

Despite calls from some in the industry that it might be time for drug manufacturers to do better when it comes to accepting the end of a drug's exclusivity period as part of a social responsibility strategy, recent actions by some – **Allergan PLC**'s deal with a Native American tribe over *Restasis* comes to mind – show the industry is continuing to pull out all the stops to protect its most valuable franchises. *(Also see "Too Bold By Half: Allergan's Latest Moves And Pharma's Leadership Deficit" - Pink Sheet, 12 Sep, 2017.)*

EXCLUSIVE CONTRACTS THAT ACT AS A PAYOFF, PFIZER ALLEGES

At the heart of Pfizer's lawsuit is a claim that J&J required insurers to sign contracts explicitly agreeing not to cover Inflectra, either at all or only in rare circumstances when patients fail treatment with Remicade first. Fail-first is just as exclusionary, Pfizer says, because doctors would not prescribe what is essentially the same product to patients who fail treatment with Remicade, but would prescribe a different product instead.

> J&J rejected the allegations. "We are effectively competing on value and price and to date, Pfizer has failed to demonstrate sufficient value to patients, providers, payers and employers."

"A key to J&J's ability to coerce insurers into accepting its exclusionary commitments is its denial of rebates to insurers that decline J&J's exclusivity commitments, thereby imposing a substantial financial penalty," the suit says. "In effect, J&J says to insurers, 'If you want to receive attractive rebates on Remicade for all of your existing Remicade patients' – rebates which, for some insurers, run into the tens of millions of dollars annually – 'you must agree to not reimburse for Inflectra, or to do so in the most limited of circumstances.'"

Insurers that decline J&J's offer face a substantial financial penalty, while those that do accept it receive what amounts to a multimillion dollar "payoff," according to the lawsuit. The tactics work largely because J&J has such a large stable of patients already on Remicade, which insurers need to cover, while Pfizer's rebates would initially be serving a much smaller group of patients, those who are new to treatment. Pfizer would have to price Inflectra below its own average variable cost to make up the lost J&J rebates and discounts.

Remicade presents specific challenges as well because it is administered through an infusion, which means providers must stock the product and pay for it upfront, relying on reimbursement from insurers to recoup the expense. Reimbursement challenges have left payers unwilling to stock Inflectra, which has trickled over to the government side of the business, even though Pfizer has secured better reimbursement under government contracts.

As of Sept. 1, about 90% of healthcare provider accounts using infliximab had not purchased any Inflectra, according to Pfizer. Additionally, Inflectra has secured less than 4% of total infliximab unit sales in the US as of Sept. 1.

"Given the cost of biologic drugs generally, and Remicade in particular, there is almost no chance that providers will pay for a product that is not widely covered by insurers for fear of stocking a product that will not be reimbursed after the provider administers it to a patient," the lawsuit maintains.

Remicade is priced at a wholesale acquisition cost of $4,000 per dose, or $26,000 per year, though J&J offers payers undisclosed rebates and discounts that reduce the costs substantially. Pfizer launched Inflectra at a 15% discount to Remicade, before undisclosed rebates and discounts.

J&J is also bundling rebates on different products in its portfolio along with Remicade, so that payers that don't accept exclusive contracts would also lose out on other portfolio rebates, according to the lawsuit.

INSURERS COWER UNDER THE PRESSURE

"Insurers have made it clear to Pfizer that its net cost for Inflectra would need to be low enough to offset the loss of J&J rebates," the lawsuit says. "Insurers have stated a desire to support biosimilars – and the lower per-unit prices they bring – but realistically cannot do so without incurring a substantial financial penalty imposed by J&J."

The lawsuit cites specific insurers, including the nation's largest, who have agreed to exclusive or fail-first contracts

for Remicade, including **United Healthcare Services Inc.**, **Anthem Inc.**, **Aetna Inc.** and **Cigna Corp.**

In the case of United Healthcare, the health insurer had published a medical policy update classifying Inflectra at parity to Remicade initially but then changed course weeks later, according to Pfizer.

Pfizer also accuses J&J of promoting the fail-first policies put in place by insurers even though there is no medical reason for them. The lawsuit includes a sample from a J&J brochure touting, "Remicade (infliximab) is preferred over Inflectra (infliximab-dyyb) at United Healthcare."

Pfizer insists tactics like the ones employed by J&J pose a risk to the entire biosimilar market, because drug manufacturers will not invest in developing the products if new entrants aren't able to break the "rebate trap" and generate a profit.

Pfizer is asking the court to declare J&J's conduct unlawful and in violation of the Biologics Price Competition and Innovation Act (BPCIA), and is requesting injunctive relief barring J&J from continuing to undertake exclusionary contracts, as well as monetary damages.

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Bold Move To Embed Biosimilar Switching Aims To Bring Savings Of Up To £300m For NHS England

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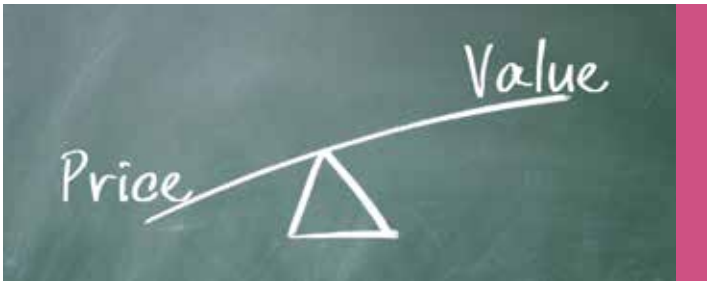

The NHS wants at least 90% of new patients to be prescribed the best value biological drug within three months of a biosimilar version being launched.

The National Health Service in England has produced a set of proposals for boosting the use of biosimilar medicines in order to generate savings of £200-300m on the drugs bill each year by 2020/21. To help reach this objective, the NHS wants at least 90% of new patients to be prescribed the "best value" biological drug within three months of a biosimilar version being launched.

NHS England said that with biological medicines currently representing the largest cost growth area in the NHS medicines budget, the aim was to "drive a step change in the uptake of biosimilar medicines by clinical commissioning groups" and to "make sure patients are offered the choice of switching to a new product by their specialist hospital doctor."

The ideas put forward in the new "Commissioning framework for biological medicines" include "embedding" the idea of biosimilar switching into commissioning and clinical practice, and offering departmental "incentives" to cover staff costs when making a switch. NHS commissioners will be required to keep abreast of upcoming biological patent expiries, and to work with patients and prescribers on biosimilar switching issues.

NHS England, for its part, says it plans to proactively communicate data on currently available biosimilars in each NHS region, as well as providing information on products that will soon face biosimilar competition. It cites in particular the example of AbbVie's *Humira* (adalimumab), which cost the NHS more than £250m in 2015/16 and will face biosimilar competition in the UK from next year. Roche's blockbuster breast cancer drugs, *Herceptin* (trastuzumab), is also in the frame. Samsung Bioepis's *Ontruzant* has just become the first biosimilar trastuzumab to be recommended for approval in the EU.

Industry bodies representing biosimilar firms were pleased with the practical approach to biosimilars being taken by the NHS. Warwick Smith, director general of the British Biosimilars Association (BBA), said the association welcomed this "clear statement" and the focus NHS England was placing on "ensuring the use and increased uptake of biosimilar medicines."

Medicines for Europe, which represents generic and biosimilar firms at European level, said the new framework "goes a long way in setting concrete objectives for the optimisation of the use of biologic medicines in the UK healthcare system". It told the *Pink Sheet* that the document showed how experience to date had "allowed us to move from theoretical discussions and potential benefits to a concrete framework where these benefits can be actually realised."

But the R&D-based industry group the ABPI was less than impressed. It said it had contributed to the drafting of the document and acknowledge the need for a framework to "increase consistent adoption of best value biological medicines and improve access for patients."

But it was "concerned that the figures for potential savings in the final document may be overstated, with the result that there will be a disproportionate emphasis on switching as the route to achieve best value. With expenditure on many of these medicines already

capped by the Pharmaceutical Price Regulation Scheme (PPRS), we would welcome greater transparency from NHS England about the data that is being used to calculate the projected savings."

MORE BIOSIMILARS ON THE WAY

The new framework was published on Sept. 12. It is a response to the fact that "over the coming months and years" more biological medicines will lose patent protection and more biosimilars will reach the market, NHS England says.

Noting that the NHS spent £16.8bn on medicines in 2015/16, up by 8% on the previous year, it says this is "a trend which is forecast to continue as new medicines enter the market and as the population ages." The NHS has the potential to realize savings of at least £200-300m per year by 2020/21 if it "embraces the use of best value biological medicines in a proactive, systematic, and safe way."

The NHS has already benefitted from significant savings on some medicines and it is "getting better at adopting biosimilars," it declares, citing pilots at the Southampton General Hospital and in the Greater Manchester region that have implemented switch programs for biologicals where the savings are invested in improving patient care locally. *(Also see "Biosimilar Confidence And Knowledge Needed In Europe, Say Experts" - Scrip, 26 Jul, 2016.)*

But "despite the two success stories above, there is evidence of significant and unwarranted variation between local areas and regions in the use of biosimilar medicines," it observes. In January 2017, for example, "one NHS Trust in central London had an uptake of infliximab of only 25%, whilst another just 16 miles down the Thames had an uptake rate of 99%. This shows that there is significant opportunity to further benefit from biosimilar medicines if action is taken across the country and best practice is implemented."

It notes that a biosimilar version of rituximab (Roche's *MabThera*) recently became available, and that in 2018 a biosimilar version of Humira will enter the market. "The NHS must ensure that it has the right commissioning framework in place to realise the potential savings benefits of a switch to these biosimilars and it is for this purpose that this framework has been developed."

"It is now important for the NHS to embed the principles of switching to the best value biological medicine into commissioning and clinical practice, if we are to realise the optimal rate and extent of savings associated with these medicines."

RESPONSIBILITIES OF COMMISSIONERS

The document places much of the responsibility for boosting biosimilar usage on the shoulders of NHS commissioners, suggesting that the proposals will help them to "act promptly to make the most of the opportunity presented by increased competition amongst biological medicines."

Shared decision-making between CCGs, clinical prescribers and patients will be vital "if the best value, clinically effective medicines are to be used," it says.

NHS England also emphasizes the need for better horizon-scanning. Commissioners and providers are expected to familiarize themselves with patent expiry dates for originator biological medicines, "and the possible launch date of individual biosimilar products." Commissioners are to work with all relevant stakeholders and plan ahead to identify the "optimum approach" in their areas so that the NHS can "remain on the front foot and prepare local systems to make the most of biosimilars."

> "Savings can be re-invested to finance improvements in pathways of care and/or innovative medicines" – Medicines for Europe

A key aim, NHS England says, is to ensure that "at least 90% of new patients will be prescribed the best value biological medicine within three months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months, or sooner if possible."

But it accompanies this exhortation with a sharp warning to commissioners: "Delivery against this ambition will be monitored, and where the 80% figure is not achievable within a CCG geography, CCGs will need to provide a written explanation to NHS England explaining the reasons why."

It adds: "We will publish information on the best and worst performers, which aligns with NHS Improvement plans on top 10 medicines and model hospital dashboard."

NHS England also suggests "appropriate financial arrangements" to encourage providers to implement processes that encourage early adoption and prescribing. These could include a "departmental level incentive to cover the cost of staff resource used in facilitating a switch to biosimilar medicine," although over time and "once the practice of best value prescribing has been embedded, we would expect incentives to cease."

Treatment decisions, it says, should always be made firstly on the basis of clinical judgement for individual patients and secondly on the basis of the "overall value proposition" offered by individual medicines. "If more than one treatment is suitable, the best value biological medicine, including biosimilars, should be chosen."

Smith said that biosimilars can save the NHS "very significant amounts of money" that can be "ploughed back into frontline care and we are already seeing examples where a specialist nurse can be funded through savings due to the use of biosimilars."

Similarly, Medicines for Europe noted NHS England's emphasis on having a systematic approach so that the most cost-effective biological drug was used. "Generated savings can be re-invested to finance improvements in pathways of care and/or innovative medicines, especially in a context where forecasts anticipate a continued growth of the pharmaceutical expenditure over the next years."

Overall, the association said, the new approach "comes as a natural step after the extensive multi-stakeholder engagement over the last years and reinforces the idea that sustainable competition in the biological medicines market can be stimulated with tailor-made national policies."

From the editors of Scrip Regulatory Affairs. Published online September 15, 2017

CHMP OKs First EU Biosimilar Herceptin, And Another Version Of Humira

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The European Medicines Agency's scientific committee, the CHMP, has given the thumbs-up to Samsung Bioepis's *Ontruzant* (formerly known as SB3), a biosimilar version of Roche's breast cancer treatment *Herceptin* (trastuzumab).

Provided the positive opinion is converted into a marketing authorization by the European Commission, this will be the first biosimilar of Herceptin to reach the EU market.

The EMA announced the positive opinion on Sept. 15, following the committee's monthly meeting this week. Ontruzant, which is indicated for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer, will be marketed in the EU by Merck Sharp & Dohme. The product was filed with the CHMP in October 2016.

Christopher Hansung Ko, President & CEO of Samsung Bioepis, said: "We are proud to see Ontruzant become the first trastuzumab biosimilar recommended for approval in Europe, where breast cancer remains the most common form of cancer affecting women. If approved, we hope Ontruzant will play an important role expanding patient access to trastuzumab across the region."

Samsung Bioepis now seems to be the clear front-runner to take on Herceptin in Europe. Mylan and Biocon had been expected to be the first to the EU market, having filed their product with the EMA in August last year.

But last month the two companies withdrew their application (along with that for a pegfilgrastim biosimilar) because of compliance problems at Biocon's Bangalore manufacturing site in India. The companies said they planned to resubmit the applications once they had completed corrective actions at the plant and undergone a re-inspection. *(Also see "More Questions As Biocon Pulls EU Filings For Two Biosimilars" - Pink Sheet, 16 Aug, 2017.)*

How far Ontruzant manages to take market share from Herceptin will depend to a large extent on its uptake in the individual European countries, whose approaches to biosimilars vary widely. Some, like Norway, have proactively sought to encourage biosimilar prescribing and switching, while others are lagging behind. Ireland, for example, has a very low uptake of biosimilars, although it is taking steps to boost prescribing levels. *(Also see "Switching, Substitution & Quotas: Irish Govt Wants Views On Boosting Biosimilars" - Pink Sheet, 11 Aug, 2017.)*

> Whether Ontruzant manages to take market share from Herceptin will depend on its uptake in individual European countries, whose approaches to biosimilars vary widely.

Celltrion also has a biosimilar trastuzumab, *Herzuma*, under review at the CHMP, and could be the next to secure a positive opinion, having submitted its dossier at the same time as Samsung Bioepis. Other companies developing biosimilar versions include Pfizer (PF-05280014) and Amgen/Allergan (ABP980); the latter product was filed with the EMA in March 2017.

BI'S BIOSIMILAR HUMIRA OKD

Another biosimilar to receive the CHMP's blessing on Friday was Boehringer Ingelheim's adalimumab product, *Cyltezo* (formerly BI 695501), a biosimilar version of AbbVie's blockbuster drug *Humira*. The product was filed with the EMA in January this year.

Two other adalimumab products are under review by the committee: Sandoz' GP2017 and Fujifilm Kyowa Hakko Kirin Biologics' FKB327 – both filings were accepted in May 2017.

Three biosimilar versions of Humira already have EU marketing authorizations: Amgen's *Amgevita* and *Solymbic* (approved in March 2017) and Samsung Bioepis's *Imraldi* (August).

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Not Just Herceptin Biosimilar: Additional 12 Drugs Set For EU Marketing Approval After CHMP Nod

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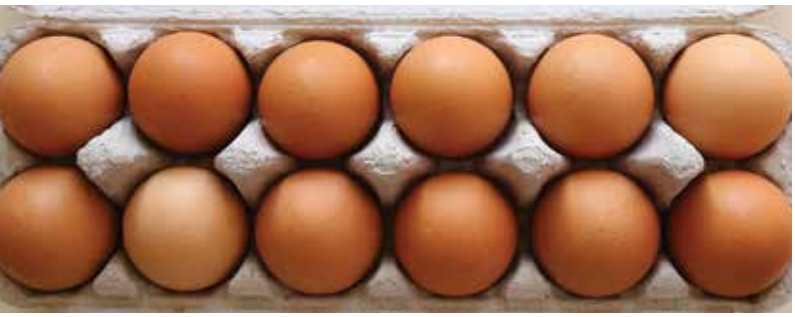

The European Medicines Agency's key scientific committee, the CHMP, has recommended for approval throughout the EU 13 of the 14 initial marketing authorization applications that it reviewed at its September meeting. Products that can now look forward to securing formal approval within months include *Ontruzan*t from **Samsung Bioepis Co. Ltd.**, the first biosimilar version of **Roche**'s blockbuster breast cancer drug, *Herceptin* (trastuzumab) recommended by the committee.

There was good news as well for **Johnson & Johnson**, **Tesaro Inc.** and **GlaxoSmithKline PLC**, among others.

Roche's new multiple sclerosis treatment, *Ocrevus* (ocrelizumab), could have got the green light, but didn't.

The CHMP's latest monthly meeting took place in London from Sept. 11–14. *(Also see "New Treatments For Psoriasis, Ovarian Cancer And MS Seeking CHMP Thumbs Up This Week" - Pink Sheet, 13 Sep, 2017.)* Also at the meeting, the CHMP upheld the three negative opinions it handed down in May to products from **AB Science**, **XBiotech Inc.** and **Helsinn Group**.

Four products will have their current indications extended. There was bad news for **Santhera Pharmaceuticals AG**, though, as the CHMP recommended denial of the company's application to extend the indication of *Raxone* (idebenone) to cover Duchenne muscular dystrophy. *(Also see "'Surprised and Disappointed' Santhera To Fight EU's DMD Rejection" - Pink Sheet, 15 Sep, 2017.)(Also see "Santhera Hopeful On EU DMD Indication Extension" - Pink Sheet, 12 Sep, 2017.)*

The following products received positive opinions:

- Ontruzant for treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer. *(Also see "Bold Move To Embed Biosimilar Switching Aims To Bring Savings Of Up To £300m For NHS England" - Pink Sheet, 15 Sep, 2017.)(Also see "CHMP OKs First EU Biosimilar Herceptin, And Another Version Of Humira" - Pink Sheet, 15 Sep, 2017.)*
- Johnson & Johnson's first-in-class interleukin-23 inhibitor, *Tremfya* (guselkumab), for the treatment of plaque psoriasis. This is already approved in the US.
- Tesaro's PARP inhibitor *Zejula* (niraparib) for the treatment of ovarian cancer. This was the only orphan drug among the recommended products. It is also approved in the US. *(Also see "Tesaro Pumped As PARP Inhibitor Zejula Gets CHMP Nod" - Scrip, 15 Sep, 2017.)*
- *Elebrato Ellipta* and *Trelegy Ellipta*, which appear to be two versions of GSK's triple combination therapy (fluticasone furoate/umeclidinium/vilanterol) for chronic obstructive pulmonary disease. *(Also see "GSK's COPD Triple Combo To Challenge Chiesi's Trimbow In EU" - Scrip, 13 Sep, 2017.)*
- Steba Biotech's vascular-targeted photodynamic therapy *Tookad* (padeliporfin), a novel tissue-preserving treatment for low-risk prostate cancer. Tookad appears to be marketed only in Mexico.
- *VeraSeal* human fibrinogen/human thrombin product, for the treatment of hemostasis, from Instituto **Grifols SA** .
- Two **Mundipharma International Corp. Ltd.** products – *Nyxoid*, a new intranasal spray formulation of naloxone for the emergency reversal of opioid overdose, and *Zubsolv* (buprenorphine/naloxone), a sublingual tablet for the maintenance treatment of opioid dependence.
- **Boehringer Ingelheim GMBH**'s adalimumab, *Cyltezo*, a biosimilar version of AbbVie's Humira for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis.
- Three generics: *Imatinib Teva*, *Miglustat Gen. Orph* and *Ritonavir Mylan*.

OCREVUS

Roche appeared before the CHMP this week to answer questions the committee still had over Ocrevus, but it seems there are still outstanding concerns. Ocrevus was approved in the US in March for relapsing multiple sclerosis and primary progressive multiple sclerosis; manufacturing worries delayed its approval there. *(Also see "Genentech's Ocrevus Manufacturing Process Still A Work In Progress" - Pink Sheet, 15 Jun, 2017.) (Also see "Ocrevus Launching Quickly Even After Manufacturing Worries Delayed US Approval" - Pink Sheet, 29 Mar, 2017.)*

Roche said: "The review of Ocrevus is ongoing, and we are working closely with the EMA to facilitate their review. We do not comment on the ongoing review of our investigational medicines, but look forward to bringing Ocrevus to people in Europe with RMS and PPMS as soon as possible."

NEGATIVE OPINIONS UPHELD

The three negative opinions that the CHMP upheld related to the following products:

- **AB Science**'s orphan drug, *Masipro* (masitinib), for the treatment of mastocytosis. *(Also see "AB Science Asks For Re-examination After EMA Rejects Masitinib For Mastocytosis" - Scrip, 22 May, 2017.)*
- **XBiotech Inc.**'s human IGG1 monoclonal antibody for the treatment of metastatic colorectal cancer.
- **Helsinn Group**'s *Adlumiz* (anamorelin hydrochloride), for anorexia, cachexia or unintended weight loss in patients with non-small cell lung cancer.

NEXT STEPS

The committee's opinions are forwarded to the European Commission for a legally binding decision valid throughout the EU. The commission usually follows CHMP recommendations, and has 67 days in which to make its decision.

CHMP plenary meetings are held monthly. The committee will next meet on October 9-12.

From the editors of Scrip Regulatory Affairs. Published online September 15, 2017

FDA

CDER Succession: Woodcock's Responsibilities Mount With No Clear #2 In Sight

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The recent departure of Richard Moscicki from the US FDA's Center for Drug Evaluation & Research shines a spotlight on the lack of an obvious succession plan for the top slot in CDER.

CDER Director Janet Woodcock has given no indication that she expects to retire from FDA any time soon. However, after 20 years leading the center for drugs – and 31 years at FDA – speculation about her departure will only continue to grow over time.

FDA has not commented on Moscicki's departure. However, if the agency replaces him, the selection will almost automatically be treated as the likely eventual successor to Woodcock as CDER director.

For the past nine months, Woodcock has been wearing two very large hats: acting director of the Office of New Drugs (since the departure of John Jenkins in January) while retaining her responsibilities as CDER director. Moscicki's decision to leave for a position at the Pharmaceutical Research & Manufacturers of America leaves one more senior slot open in CDER without an obvious successor.

At the time Moscicki was recruited to FDA, the newly created (and third) deputy position was widely presumed to be reserved for an heir-apparent to Woodcock. The selection of Moscicki, then nearing 60 years old after a 20-year career at **Genzyme Corp.**, dampened some of that speculation. *(Also see "CDER Taps Genzyme Exec As Deputy Director For Science Operations" - Pink Sheet, 12 Feb, 2013.)*

Janet Woodcock

After nearly a year at FDA, OND deputy Peter Stein is likely adjusting to his move (and about to move past the period where he is precluded from participating in issues related to Merck).

Moscicki never really developed a defining role inside CDER. He had an obvious interest in rare disease regulation from his days at Genzyme, and his own drawn-out hiring process led Woodcock to tap him to lead an initiative to recruit senior managers from industry. Moscicki had some success: **Merck & Co. Inc.**'s Peter Stein joined FDA as deputy director of the Office of New Drugs in 2016, just one month before Jenkins' departure after another long hiring process. *(Also see "Merck R&D Exec Jumps To US FDA As Office Of New Drugs Deputy Director" - Pink Sheet, 8 Nov, 2016.)*

When Woodcock decided to take over OND earlier this year, it might have been a perfect opportunity to name Moscicki acting CDER director or otherwise elevate his role – all the more so since Woodcock's decision to take over as acting OND director had the feel of a valedictory project to implement some changes in the new drug review model.

Instead, Moscicki is leaving the agency.

The two remaining deputy CDER directors – Bob Temple (Clinical Science) and Doug Throckmorton (Regulatory Programs) – are not viewed as likely to succeed Woodcock.

After 45 years at FDA, Temple has an unsurpassed level of institutional knowledge, but his role at the agency has evolved away from direct management to a senior advisor role. Throckmorton has 20 years at FDA, and would be the more obvious choice to eventually lead the center. He has testified frequently on behalf of CDER at Congressional hearings, a sure sign of Woodcock's trust and respect.

However, Throckmorton was already a deputy at the time CDER created the new position eventually filled by Moscicki – raising the question why Throckmorton wouldn't have been designated as a principal deputy at the time if Woodcock saw him as a likely successor.

Within FDA, the belief is that Woodcock is not the type of manager to end her tenure – assuming she would have influence over her successor – without a clear (and hand-picked) replacement. In that sense, Moscicki's departure is the latest sign that Woodcock has no plans to leave the agency any time soon.

The Office of New Drugs director position may be the easier – and nearer-term – position to fill. OND has a deputy in Peter Stein, who after nearly a year at FDA is likely beginning to adjust to his move to government (and to move past the period where he is precluded from participating in issues related to his former employer).

Stein serves as chair of the biosimilars committee, is a member of the Medical Policy Council and has projects under the change management initiative. But he also has no signatory authority; that is reserved at the office and division level, with Woodcock holding veto power – as demonstrated in the decision to approve **Sarepta Therapeutics Inc.**'s *Exondys 51* (eteplirsen).

In one potential scenario, Woodcock could launch a national search for OND, with Stein as one of the applicants. There also a number of lower-level officials that could conceivably be candidates to be director of OND, but none appear to the obvious choice.

Whoever is selected to head OND, the new director may end up having a more profound impact on the performance on drug reviews than any potential change at the top of CDER might. In the months leading up to his departure from OND, Jenkins formally questioned Woodcock's fitness to head the office, which she had indicated she would do after he retired. Jenkins cited what he thought was Woodcock's "bias" and excessively close involvement in the eteplirsen review. *(Also see "Woodcock's 'Bias' In Sarepta Case Made Jenkins Worry About Future Drug Reviews" - Pink Sheet, 31 Jul, 2017.)*

FDA leadership has stood steadfastly behind Woodcock during the controversy, but if the OND rank and file share the concerns about her that Jenkins expressed in his memo to then-Commissioner Robert Califf, staff morale may need to be a consideration as Woodcock, and other FDA officials, contemplate who should be the next head of OND.

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CLINICAL TRIALS

US FDA To Publish Own Datasets In Latest Signal Of Enhanced Transparency

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The US FDA is looking to routinely publish clinical data used in regulatory decision making along with adverse event reporting data, in what appears to be just the latest effort of Commissioner Scott Gottlieb's high profile effort to enhance transparency at the agency.

Speaking at the POLITICO Pro Summit Sept. 14, Gottlieb explained that sometimes FDA develops its own datasets based on submitted datasets from sponsors to help the agency make its own decisions. The agency is looking to make such clinical information available if it has "public health relevance," Gottlieb says.

"My view is that if we are developing a novel dataset that we are using for regulatory decision making, we ought to think about how we provide public access to that, because it is becoming a regulatory tool we are using, people should be able to query it and assess our work," Gottlieb said.

The commissioner admitted there will be some difficulties publishing certain data, such as issues with informed consent, which the agency will need to be mindful of as it pursues the initiative.

What's more, Gottlieb said FDA is also looking to allow for "more wholesale access" to adverse event reporting data that is submitted to the agency. Gottlieb noted that clinicians sometimes have difficulties searching for such data.

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to the agency. Users can search FDA's website for statistics on the numbers of reports submitted to the agency for drugs over the past 10 years. Currently, however, one must be familiar with creation of relational databases to search the raw data consisting of individual case safety reports.

REMS LETTERS TO COME AS WELL

Gottlieb also confirmed that FDA will "very soon" be publishing letters sent to brand drugmakers that inform them it is permissible to sell products with a risk evaluation and mitigation strategy (REMS) to generic sponsors for bioequivalence testing.

REMS abuse has been an issue Gottlieb has spoken on several times since his confirmation as commissioner in May. He first floated the idea of the public shaming tactic at a July meeting on the Hatch-Waxman Act. *(Also see "FDA Exploring Whether Public Shaming Can Stop REMS Abuses" - Pink Sheet, 18 Jul, 2017.)*

"Right now, those letters are sent directly to the branded companies and the generic sponsors," Gottlieb said. "That is another place we are going to provide more transparency. We think that's important in this case for promoting competition in the market. And we think competition is a matter of public health."

Gottlieb has also discussed how the agency is looking at its own internal options to address the issue of REMS abuse. *(Also see "Gottlieb Talks Activist Role For FDA In Curbing REMS Abuse" - Pink Sheet, 20 Jun, 2017.)*

A NEW LEVEL OF TRANSPARENCY?

Since taking the reins of FDA in May, Gottlieb appears to be promoting a level of transparency at the agency beyond that of his predecessors, with his remarks at the POLITICO Pro Summit just being the latest example.

In addition to efforts in making data more publicly available, Gottlieb has been very active over the past few weeks alone personally making public appearances to discuss the future of the agency.

At the Regulatory Affairs Professionals Society Regulatory Convergence Conference on Sept. 11, Gottlieb announced that the agency will begin working on 10 new disease-specific development guidance documents over the next year as part of FDA's steps on the clinical front to help make drug development more efficient. *(Also see "FDA's Gottlieb Pushing 'Seamless' Clinical Trials For Faster Development" - Pink Sheet, 11 Sep, 2017.)* He also noted that he would like the agency to conduct more systemic reviews of its regulations. *(Also see "Gottlieb Wants More Systematic Updates Of Regulations" - Medtech Insight, 12 Sep, 2017.)*

Gottlieb also said FDA is also looking to allow for "more wholesale access" to adverse event reporting data that is submitted to the agency.

The next day at a Friends of Cancer Research meeting the following day, Gottlieb announced that one of the disease-specific guidances will include Alzheimer's. *(Also see "Alzheimer's Guidance Coming From US FDA, Part Of Broader OND Reform" - Pink Sheet, 14 Sep, 2017.)*

Speaking at Research America's National Health Research Forum Sept. 7, Gottlieb explained that the agency may require less preclinical data for certain second entry therapies that involve new technology platforms. *(Also see "Gene Therapy Platforms May Require Less Preclinical Data, Gottlieb Says" - Pink Sheet, 7 Sep, 2017.)*

Gottlieb is also scheduled to speak Sept. 29 at the National Press Club about modernizing the role of FDA's medical staff.

Additionally, Gottlieb has also outpaced his most recent successors in appearing in FDA press statements. Since taking over the commissioner role, there have been 24 total statements that are either entirely attributable to Gottlieb or contain a quote from him. That number tops Robert Califf's total of seven over his first four months, and Margaret Hamburg's total of 20 during the same timeframe.

Gottlieb has already topped Califf's total number of FDA media release appearances, as the Barack Obama appointee appeared in 13 total statements during his roughly 11 months as the head of the agency.

The large number of press release appearances from Gottlieb may be due in part to 2017 being a year of user fee renewals, warranting comments from the new commissioner.

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Clinical Trial System 'Broken,' But Modernization Long Way Away – Woodcock

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Center for Drug Evaluation and Research (CDER) Director Janet Woodcock described the current clinical trial system as "broken" in that it discourages new drug development, but admitted that it will likely be a long time before modernization of the system can take place.

Speaking Sept. 20 at a National Academies of Sciences, Engineering, and Medicine meeting on real-world evidence, Woodcock stressed the need for a new way to study drug products, as randomized clinical trials do not always fit well with studying areas such as rare diseases.

"Our inability to generate the needed evidence efficiently and in a cost-effective manner will continue to be a barrier to innovation and to quality of care around the world," Woodcock said.

"We need to bring the clinical trial universe and the healthcare universe as close together as possible," Woodcock said. So much of the work is done in the actual process of care in the trials to reduce costs and improve efficiency.

Woodcock touted the use of a "hybrid" approach that modernizes the development of both new drugs and supplemental indications. She specifically pointed to the use of master protocols and platform trials as essential parts of the future for this type of development.

"Because they are continuous, rather than start and stop, they could add elements to incorporate data collection and trial procedures into the care process," Woodcock said. "And thus the characteristics of real-world evidence.

"There's no reason this type of trial could not be done for regulatory purposes."

Although groups in the US and Europe are working on ways to integrate electronic health data into the trial system, it will be a long time until such a practice becomes the norm, Woodcock said.

US FDA Commissioner Scott Gottlieb explained the current difficulties of leveraging

electronic data in remarks the previous day. Such data are incentivized to be structured in ways geared toward billing, meaning that relevant clinical information about patients is often found in "unstructured notes."

CALIFF: MORE PRECISION CAN MAKES THINGS WORSE

Former FDA Commissioner Robert Califf also spoke of modernizing clinical trial practices earlier in the day during his keynote address. He called for a shedding of the old system that "has gotten bloated and burdened with practices that are not only more expensive, but also I think actually making things worse."

"[The old practices] massively increase the cost without improving quality, and sometimes make quality worse, because the standard operating procedures have become more important than the science of clinical investigation," Califf said.

The former commissioner, now back at Duke and director of a new center focused on integrated health data science, specifically pointed to the mistaken notion in clinical practice that recording each data item more precisely will result in a more reliable estimate of treatment effect. Many in industry have the mindset of, "Well, because it's safety, it means we have to do stupid stuff that costs a fortune to show people that we are really concerned about safety," Califf says, even though that is not the intended mindset of regulators with regard to clinical practice.

"Until we get that point across, we are going to continue to waste hundreds of millions of dollars," Califf said, adding that a refocus on quality of design, automation and analytical methods should help to accelerate the generation of evidence while improving results.

THE FATE OF GCP?

The meeting also featured debate about the future of Good Clinical Practices (GCPs) on the clinical trials scene, which Califf had described as "not good, not clinical, and not practical."

Rory Collins, a professor of medicine and epidimeology at Oxford University, made the analogy of Dr. Frankenstein creating a monster, with the proper way to kill a monster being "a stake through the heart."

"What we need are guidance for the twenty-first century, which does talk about using electronic data systems in the appropriate way, which does involve randomization in a whole series of areas," Collins said. "And I think while we've still got this nineteenth century set of guidance, it is going to be very difficult to do that. So I would pull the plug on it."

Woodcock, however, did not support scraping any of FDA's International Conference on Harmonization (ICH) guidances on the subject. She explained that the agency's regulations are in place for the "bottom one percent" of actors that make the entirety of industry look bad.

"You wouldn't believe what some people will do," Woodcock said. "And they do it. And so we have to have rules that do protect people, because there are what I call bottom feeders out there, and those people will do things that will astonish anyone."

Woodcock said these actors pose issues for patient safety and disincentive people from enrolling in trials. To avoid having no rules for a period of time, FDA needs to instead needs to propose efforts to modernize the approach, the CDER director said.

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Mexican, Turkish And Iranian Inspectors Become Latest Members Of PIC/S

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Drug regulators from Mexico, Turkey and Iran are to become the newest members of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), which currently involves 49 authorities from 46 countries working to harmonize manufacturing inspection procedures worldwide.

Mexico's agency COFEPRIS, the Turkish Medicines and Medical Devices Agency and Iran's Food and Drug Administration will start to participate in the scheme on Jan. 1, 2018, the PIC/S said.

The three agencies were invited to join the scheme during the Sept. 11-12 PIC/S Committee meeting in Taiwan, having cleared the lengthy pre-accession and accession application stages. Their acceptance on the scheme enables them to work on PIC/S topics with existing member authorities from countries such as Argentina, Australia, Canada, Croatia, France, Germany, Israel, Italy, Japan, Norway, Spain, South Africa, Sweden, Taiwan, Thailand, the UK and the US.

EARLY DAYS FOR RUSSIA

Also during the meeting, rapporteurs were to be appointed to start the assessment process for Russia – the latest country that has applied to join the scheme. Russia's application for pre-accession to the PIC/S was submitted jointly by the country's Ministry of Industry and Trade (Minpromtorg), which is in charge of domestic good manufacturing practice (GMP) inspections, and the State Institute of Drugs and Good Practices, in charge of foreign GMP inspections.

Russia is one of three countries in the PIC/S pre-accession stage, which serves to identify any gaps between PIC/S membership requirements and the system used by the applicant's competent authority; the other countries are Kazakhstan and Saudi Arabia. Based on the gap analysis, the PIC/S Committee decides whether, for example, to invite the authority to apply for membership by submitting an application for the PIC/S accession stage.

The PIC/S, which was established in 1995 as an extension to the Pharmaceutical Inspection Convention of 1970, is open to any authority that has a comparable GMP inspection system. It aims at harmonizing inspection procedures worldwide by developing common standards for GMP and providing training opportunities to inspectors.

For example, last year it launched a six-month trial implementation of a guideline that could set the standard globally for enforcing data integrity in pharmaceutical manufacturing. *(Also see "49 PIC/S Inspectorates Test-Drive Data Integrity Guidance" - Pink Sheet, 23 Aug, 2016.)*

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Janssen Deal Could Signal Clinical Trial Revival In Argentina

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A new agreement between **Janssen Inc.** and Argentina's health ministry signals a revival of investments in clinical research in the country, thanks to new regulations that have removed bureaucracy and improved time lines, according to the health ministry.

Janssen will increase its investments in clinical research in the country to $78m between 2017 and 2020 in a move that will generate around 3,000 jobs. The investment is recognition of changes introduced by medicines regulator ANMAT to regulations on good clinical practice, according to health minister Jorge Lemus.

Roy Benchimol, general manager of the Janssen Latin America said that the "new regulations have given us the opportunity to be more competitive on a global level and have a different conversation with headquarters about bringing investment to Argentina and exploiting all the scientific potential – human and technological – in the country."

Argentina was traditionally an important market for clinical trials, according to Enrique Rodríguez Chiantore, head of the government's advisors on health. Some 15 years ago the country hosted 2.5% of the world's clinical studies, but this figure has since fallen to 0.8% because of bureaucratic difficulties, he said. However, he added that the new regulations "are generating a new stream of studies and investment."

"New regulations have given us the opportunity to be more competitive on a global level and have a different conversation with headquarters" - Janssen

THE REGULATIONS

Regulations 4008/2017 and 4009/2017 were published in the official Gazette on May 4, 2017. They both amend regulation 6677/10 which set out rules on good practice for clinical pharmacology studies to guarantee compliance with national and international legal and ethical standards.

Regulation 4008 shortens timelines, for example it reduces the period for reviewing documentation submitted by sponsors from 90 working days to 70 working days (this includes 60 days for review, then a further ten days for administrative processes.) Among other things, it also sets a three-working day deadline for the medicines evaluation and registration board to verify initial documentation submitted in support of study approval requests.

Meanwhile, regulation 4009 sets out infrastructure and staff requirements for sites for Phase I and bioequivalence studies. This also replaces regulation 3598/02.

According to FECICLA, the foundation for ethics and quality in Latin American clinical research, "the new regulations are a big step forward for the country as they commit authorities to improving evaluation processes without affecting their rigor … and they align regulations with the most advanced regulations for protecting subjects taking part in Phase I studies."

The agreement, inked on Sept. 8, will also see the health ministry and Janssen co-operate on joint actions on disease treatment and prevention, among other things.

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Pfizer's Sutent Expanded Indication: 'Hope' Or 'False Hope'?

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The US FDA's Oncologic Drugs Advisory Committee, just like the agency itself, struggled to determine whether **Pfizer Inc.**'s *Sutent* (sunitinib) provides clinical benefit as an adjuvant treatment of renal cell carcinoma, offering no definitive recommendation.

The committee tied with a 6-6 vote Sept. 19 on whether the risk-benefit profile was acceptable as adjuvant treatment in RCC patients at high risk of recurrence following nephrectomy.

Pfizer is seeking to expand the RCC indication in the Sutent label. The tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) already has been approved for treatment of advanced RCC, as well as gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate, and progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.

A vote or two pushing the majority to a positive recommendation likely would not have been a clear signal that FDA approval was imminent, given the agency's own questions about the clinical data. Still, would have been an encouraging sign for the application. In this case, it appears a tie may not favor the runner, unlike in baseball.

FDA HAD SAME INTERNAL DEBATE

Unfortunately for FDA, the committee did not offer much help for the approval decision.

Richard Pazdur, director of FDA's Oncology Center of Excellence, joked after the vote that he was glad the committee reached a consensus, because it makes FDA's job infinitely easier.

Pazdur also said agency reviewers had the same debates as the committee, which is why the application was sent to ODAC for consideration.

"I'm somewhat happy to see that we're not isolated in our own questions that we have regarding this application," he said.

A DIFFICULT QUESTION

Pfizer said in a written statement that it was encouraged by the committee discussion and would work with FDA as it is incorporated into the review.

Advisory committee members admitted the decision was difficult. Some tried to answer the question using unmet need arguments, while others said the data was not conclusive.

Committee patient representative Richard Lumley said he voted the risk-benefit ratio was favorable because he felt Sutent would provide patients some "hope."

But then consumer representative Courtney Preusse, of Fred Hutchinson Cancer Research Center, said she voted No because she thought Sutent would give patients "false hope."

"I feel that the data is immature. I feel that there are still too many questions to be answered," she said. "Elevating this drug out of clinical trial status and to full FDA approval would somehow elevate it above all other investigations that are currently ongoing in clinical trials. And I don't feel that it's in a place right now where it can be elevated."

Statistical issues also complicated consideration of the application supplement.

Pfizer's S-TRAC trial showed a statistically significant increase in disease-free survival in patients on Sutent compared to placebo. But the ASSURE trial, which was conducted by the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group, showed no difference in disease-free survival in the Sutent arm compared to placebo in the adjuvant setting. Exploratory analyses using data from both trials also were mixed, raising

> FDA reviewers had the same debates about the disparate trial results as the committee, which is why the application was sent to ODAC.

> The statistical issues were so complicated that FDA approved conflict of interest waivers to ensure ODAC had enough statistical expertise to understand them.

questions about the S-TRAC results.

The statistical issues were so complicated that FDA approved conflict of interest waivers to ensure ODAC had enough statistical expertise to understand them. *(Also see "Pfizer Sutent Label Expansion May Hinge On Disease-Free Survival Stats" - Pink Sheet, 10 Sep, 2017.)*

Interestingly, Pfizer helped fund both trials. *(Also see "Pfizer v. Pfizer: Sutent Indication Expansion Will Hinge On Conflicting Trials" - Pink Sheet, 17 Sep, 2017.)*

PENALIZING PFIZER FOR NOT MATCHING ANOTHER TRIAL'S RESULTS?

Ramaprasad Srinivasan, head of the molecular cancer therapeutics section at the National Cancer Institute Center for Cancer Research, said S-TRAC suggested that patients should at least be able to consider using Sutent as adjuvant therapy. He voted that the benefit-risk ratio was acceptable.

Many the committee members acknowledged that S-TRAC was well-conducted. Philip Hoffman, of the University of Chicago Department of Medicine hematology/oncology section, who voted the risk-benefit ratio was favorable, said Pfizer should not be penalized because its results did not match the ASSURE study.

"With appropriate selection and management of toxicity I think that it's reasonable to approve it," he said.

But Bruce Redman, of the University of Michigan Comprehensive Cancer Center, voted No and said he did not see data that indicated he could tell a patient that using Sutent in the adjuvant setting would delay disease recurrence.

Lance Pagliaro, of the Mayo Clinic oncology department, also voted No. He said he could not say for sure that using Sutent was better than the standard of care in the setting, which is giving patients the opportunity to remain disease-free without treatment and then treat to those that need it.

"I think that in light of all the evidence we've seen today, the patients are still best served by taking that wait-and-see approach," he said.

FDA, of course, can't wait for too long to make its decision. The review goal for the Sutent supplement is January 2018.

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FDA's NDA And BLA Approvals: Adzenys ER, Solosec

Below are FDA's original approvals of NDAs and BLAs issued in the past week. Please see key below chart for a guide to frequently used abbreviations

SPONSOR	PRODUCT	INDICATION	CODE	APPROVAL DATE
New Drugs				
Neos	Adzenys ER (amphetamine)	Treatment of Attention Deficit/ Hyperactivity Disorder (ADHD) in patients 6 years and older.	S. 3	9/15/2017
Symbiomix	Solosec (secnidazole)	Treatment of bacterial vaginosis in adult women.	P, 1	9/15/2017

KEY TO ABBREVIATIONS	
Review Classifications	**NDA Submission Classification**
P: Priority review **S:** Standard review **O:** Orphan Drug	**1:** New molecular entity (NME); **2:** New active ingredient; **3:** New dosage form; **4:** New Combination; **5:** New formulation or new manufacturer; **6:** New indication; **7:** Drug already marketed without an approved NDA; **8:** OTC (over-the-counter) switch; **9:** New indication submitted as distinct NDA – consolidated with original NDA; **10:** New indication submitted as distinct NDA – not consolidated with original NDA

UK's NICE Backs BMS's Opdivo In Lung Cancer, But Only Via CDF With Price Cut

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While still refusing to make Bristol-Myers Squibb's *Opdivo* (nivolumab) routinely available on the National Health Service in England and Wales, NICE has decided upon reflection to make the PD-1 inhibitor available to certain lung cancer patients through the controversial Cancer Drugs Fund, at a cut price, whilst more evidence is gathered on its value.

Opdivo is already available in Scotland.

The decision by the National Institute for Health and Care Excellence leaves Opdivo's rival and fellow PD-1 inhibitor, **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab), leading the pack after winning backing last December from NICE for non-small-cell lung cancer, thanks to a price discount. Both medicines are monoclonal antibodies targeting a receptor on the surface of lymphocytes known as the programmed cell death protein-1 (PD-1) receptor.

Merck's Keytruda is currently recommended for routine use in non-small-cell lung cancer via a commercial access agreement with NHS England to provide it at a confidential discounted price. NICE has also recommended Keytruda for use in untreated lung cancer via the Cancer Drugs Fund.

OPDIVO'S JOURNEY

NICE last year issued draft guidance which said Opdivo was not cost effective for all patients with squamous and non-squamous advanced non-small cell lung cancer. The HTA noted at the time that the PD-1 inhibitor appeared to benefit some patients more than others.

Last October, NICE recommended that Bristol should make a case for having the drug listed on the Cancer Drugs Fund while more information was gathered on whether the drug is cost-effective in patients with tumor PD-L1 levels of 10% or more. NICE pointed out then that clinical-effectiveness data suggested that Opdivo was more effective than docetaxel for subgroups in which PD-L1 expression levels are above 1%, 5% and 10%, compared with subgroups in which the PD-L1 expression level was below these thresholds.

> "Nivolumab is clinically effective for some people with lung cancer, but the full extent of its benefit is not clear."

Bristol-Myers Squibb Co. subsequently offered the HTA body a confidential discount on the list price and put forward a further submission that included new evidence, as well as a Cancer Drugs Fund proposal to explore the benefit of Opdivo beyond three years, according to PD-L1 levels.

NICE said its appraisal committee concluded that the case was not strong enough for making Opdivo routinely available on the NHS, but that as trials were ongoing, the committee felt it would be appropriate to include Opdivo in the Cancer Drugs Fund.

Carole Longson, who heads NICE's center for health technology evaluation, said in a statement: "We know that nivolumab [Opdivo) is clinically effective for some people with lung cancer, but the full extent of its benefit is not clear. This new deal means that we can give patients access to what we know is a promising treatment whilst more evidence is gathered on its value."

NICE said Opdivo will be available from Sept 20. in England and Wales to some people with advanced non-small cell lung cancer if they have already been treated with chemotherapy. It is given intravenously in hospital every two weeks.

At its full price, Opdivo costs £439 per 40-mg vial. Exact treatment costs depend on a person's weight and his/her type of lung cancer. Under the deal, for someone weighing 73 kg, a month's treatment would cost £5,268 ($7,139). The drug will be available on the NHS at a reduced cost to reflect the clinical uncertainty, NICE said. Some 1,300 patients with lung cancer are expected to receive Opdivo as part of the deal.

Excluding any discount, Keytruda is available at a cost of £1,315.00 per 50 mg vial and the average cost of a course of treatment is estimated to be £29,114.

In June, the Scottish Medicines Consortium approved Opdivo. A spokesperson for NICE said that Scottish decision had no bearing on the NICE recommendation.

NICE is looking at Opdivo in a number of different cancer indications. Each appraisal is independent and will compare the clinical- and cost-effectiveness of the drug compared with what is already available on the NHS in that area, the NICE spokesperson explained.

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Boehringer Navigates 'Impractical' Nintedanib Surveillance Plan In India

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Boehringer Ingelheim has underscored the unviability of a mandated active surveillance plan in India for nintedanib, indicated for the treatment of idiopathic pulmonary fibrosis (IPF). The drug has also been approved for non-small cell lung cancer (NSCLC) in India.

Boehringer was previously granted permission to import and market nintedanib soft gelatin capsules 100mg/150mg for IPF with a local trial waiver (global trials though included some Indian patients), subject to the condition that it conducts an active surveillance of all the patients using the drug for two years from the date of marketing the drug. An active surveillance is typically a post-marketing surveillance but in an active way, with a structured protocol, and the aim of capturing information right from baseline and then following up the patients.

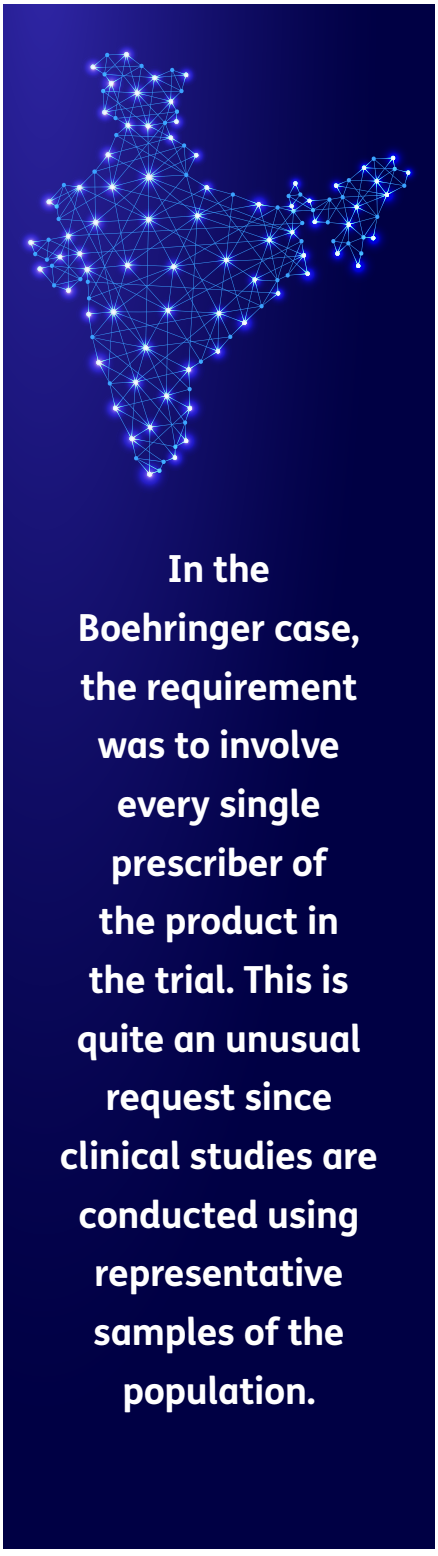
In July 2016, a subject expert committee (SEC), an expert panel which advises the Indian drug regulator on trial-related approvals, recommended that "all the prescribing physicians must participate in active surveillance and safety reporting of this drug for an initial period of two years".

Details of a SEC (pulmonary) meeting late last month, however, suggest that Boehringer has since indicated that it is "practically not possible" to ensure participation of all prescribers in the active surveillance and safety reporting for nintedanib and sought a modification of the condition.

SOME PHYSICIANS LESS KEEN TO PARTICIPATE

"Generally, some physicians in and beyond key cities have been less keen to participate and as a responsible organization, we have informed the SEC about the same," Viraj Suvarna, Boehringer Ingelheim India Pvt. Ltd's medical director, told the *Pink Sheet*.

The SEC appears to have taken note of Boehringer's request, and at its Aug. 31 meeting recommended that the active surveillance be conducted in "at least 200 patients" and that the firm should submit a status report annually. But Boehringer now appears to suggest that even these patient numbers may be high.



In the Boehringer case, the requirement was to involve every single prescriber of the product in the trial. This is quite an unusual request since clinical studies are conducted using representative samples of the population.

On the revised patient numbers specified by the expert panel, Suvarna said that while the SEC's criteria to have a "finite number of patients" for active surveillance is "rational", it would have been "more feasible" if the number of patients required to be a part of the active surveillance for certain rare disorders like IPF would have been reduced.

Boehringer also clarified that there is no longer a time-limit for the active surveillance and the SEC has not specified any time frame within which the company needs to provide real-world data of the 200 patients in IPF. "But Boehringer is required to provide an interim status report every year," the company added.

UNUSUAL REGULATORY REQUIREMENT?

While it's probably not unusual to seek post-marketing surveillance protocol tweaks, some industry experts suggest that India's SECs must, in general, use due diligence to accept only those changes that are "genuine" and "not every request." A health activist similarly sought more studied vetting of such requests, in general.

These experts tell the *Pink Sheet* that it is likely that when the initial SEC recommendations are made, companies, in general, either do not apply "due rigor" in evaluating them before accepting them, or are aware that opportunities are available for an appeal to change the requirements later on.

"In the Boehringer case, the requirement was to involve every single prescriber of the product in the trial. This is quite an unusual request since clinical studies are conducted using representative samples of the popu-

lation (prescribers or patients). While it is difficult to say why such a request was made, Boehringer should have clarified at the outset that the request was unreasonable and asked for a change," said an industry expert previously with a frontline multinational firm in India.

The expert added that the fact that the SEC modified its requirement to an evaluation of 200 patients suggests that the drug may not be indicated for "wide use", which can mean that very few doctors will use it. This, the expert claimed, should probably have made it possible for Boehringer to "satisfy the initial requirement criteria".

"It is important that SECs use their discretion and filter out routine challenges to its criteria and lay down strict guidance to define only genuine requests that they will consider. After all, the good health of the Indian citizen is in their hands."

SEC EXPERTISE

Some other industry experts though argue that Boehringer has only asked for certain changes and not a waiver of the PMS study.

"Medically the condition [IPF] is quite uncommon. Hence, even 200 subjects could be difficult to recruit," the former head of an Indian CRO told the *Pink Sheet*.

The official also noted that while international regulations on post-marketing surveillance are defined and based on "non-intervention prescription based study", regulations in India are "not very clear", though he provided no specifics.

The official also raised some concerns around the general expertise of SECs and the processes followed by these panels – a seemingly continuing pain point for industry and trial applicants. Industry has in the past referred to how SEC members do not always know the regulatory process very well and that there is generally no structure to conduct their meetings. Moreover, an inadequate level of preparation by SEC members, at times, ends up in suggestions which may be tough to implement and then require multiple rounds of discussions.

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Diagnosing A Healthy US FDA: The MRI Drug Safety Review

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Anyone looking for signs of the extraordinary regulatory climate for innovators isn't likely to start with a day-long advisory committee to discuss theoretical risks associated with gadolinium used in MRI contrast agents.

Given all the approvals (33 NMEs and counting!) or the specific breakthroughs (the first CAR-T therapy!) it is easy to describe the strong climate as the US FDA saying yes to new therapies. But it is important to remember that the current climate emerged from a difficult period defined by difficult drug safety problems—and by FDA's struggles to address them in a way that the public at large found credible.

That's why the Sept. 8 Medical Imaging Drugs Advisory Committee is an important marker of the current strength and confidence of FDA's drug review group.

The committee met to discuss the discovery that gadolinium may be retained in the brain (and other tissue) after an MRI scan, and the theoretical risk that gadolinium retention may pose. FDA initially publicized reports of gadolinium retention in the brain as a potential safety issue in 2015, and updated on the issue with a drug safety announcement in May, noting that its investigation has found no evidence of adverse health effects.

FDA was unusually explicit in framing the meeting as an attempt to seek validation for its relatively limited response to the potential risk. The two voting questions essentially asked the committee to endorse FDA's approach, which the committee did by a wide margin. *(Also see "Warning Label For Gadolinium Contrast Agents Gets US FDA Panel Backing" - Pink Sheet, 10 Sep, 2017.)*

For anyone with a long enough memory, however, it is easy to imagine things going quite differently.

The public review of the issue responded to two important external factors. First, the European Union has taken a more conservative approach, proposing to withdraw a group of products classified as "linear" (rather than "macrocyclic") agents. Second, there is an organized advocacy organization – the Lighthouse Project – calling for action to recognize and respond to gadolinium toxicity.

The history of the MRI safety issues is somewhat analogous to long-standing concerns from patients about ill-defined systemic toxicity with fluoroquinolone antibiotics. *(Also see "Break-Point: FDA Committee Votes To Restrict Quinolones, But Does Not Endorse Disability Syndrome" - Pink Sheet, 17 Nov, 2015.)*

The 2017 MRI review follows the model of a 2015 advisory committee review of the fluoroquinolone issue, suggesting that FDA has developed a playbook of sorts to deal with organized communities of self-identified victims of drug toxicities – even if there does not appear to be a plausible mechanism to explain the perceived harms.

The meeting featured a lengthy open public hearing with testimonials from patients who say they have experienced systemic toxicity after receiving a gadolinium therapy, most of whom cited a connection with The Lighthouse Project. Their testimonies were similar to the pa-

tient experiences with fluoroquinolones presented during the November 2015 safety review of that class – a shared belief in debilitating, long-term toxicity from a short-term therapy, but with diffuse, disparate symptoms.

In both cases, the patient testimonials provided a basis for the committee to support labeling changes for approved products and to call for further research. But in both cases FDA also carefully framed the votes as endorsing planned regulatory action that stopped far short of acknowledging a cause-and-effect relationship between the drug and the perceived harm.

The recent extreme weather may have helped FDA minimize the publicity associated with the gadolinium review: one of the patient testimonials was delivered on behalf of Gena Norris, wife of movie actor Chuck Norris. They had planned to attend the meeting in person but instead stayed in Texas following Hurricane Harvey.

The successful formula for the meetings depended in part on convening a review of a crowded therapeutic class. That simultaneously precluded explicit discussion of individual safety and efficacy profiles while also filling the agenda with a lot of a material from multiple sponsors.

The most important difference between the quinolone and MRI safety reviews may be in the commercial dynamics. The quinolone review went before the committee when most of the ingredients were off patent, with no meaningful difference in the perspective of the brand sponsors.

The MRI safety issue involves commercially important therapies and a group of sponsors with somewhat different perspectives – essentially a divide between sponsors who might benefit from curtailed used of the "linear" agents and those that would not.

But it did not feature any internal disagreements in the FDA review, nor did it produce follow-up headlines about FDA sweeping an important safety issue under the rug. Instead, it felt like a regulator working through an important issue without over-reacting.

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Payers Could Guarantee Biosimilar Market Share, FDA's Gottlieb Suggests

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US FDA Commissioner Scott Gottlieb is suggesting that biosimilar adoption – and development of future products – can be aided by payers setting aside a portion of sales that will go to biosimilars.

Speaking at the at the Sept. 18 Chasing Cancer Summit hosted by the Washington Post, Gottlieb was asked about the uptake of biosimilars by healthcare providers. He acknowledged that their adoption has been slow as providers are reluctant to switch patients from a therapy to a biosimilar or embrace a biosimilar as an initial treatment. FDA is conducting public education campaigns to educate providers about the robustness of the process that biosimilars go through.

Gottlieb also suggested that payers could help boost the use of biosimilars.

"This is an opportunity where payers might have a role to play by guaranteeing perhaps some market share to some of the biosimilars that are coming onto the market and then driving the adoption themselves," he said.

SLOW ADOPTION COULD SLOW DEVELOPMENT

"What I worry about is that if the adoption rates continue to be slow then the potential manufacturers of biosimilars won't see this as a viable opportunity and won't make the investments in the first place. If they don't think that they can capture 20% or 30% of market share within the first five years of being on the market, or whatever the economic model is, they might say this is a category we're going to stay away from," Gottlieb added. "If we don't think a little bit differently about this and do something potentially disruptive it could be a very slow ramp."

The importance of payers in the marketing of biosimilars was highlighted shortly after Gottlieb made his remarks when **Pfizer Inc.** filed a lawsuit against **Johnson & Johnson** on Sept. 20 alleging J&J sought to block sales of Pfizer's *Inflectra* (infliximabe-dyyb), a biosimilar to J&J's *Remicade* (infliximab). Pfizer claims J&J coerced payers by vowing to withhold all Remicade rebates if any In-

flectra is reimbursed.

FDA has approved seven biosimilars, three of which have been launched in the US: Inflectra; **Samsung Bioepis Co. Ltd./ Merck & Co. Inc.**'s Remicade biosimilar *Renflexis*; and **Sandoz Inc.**'s *Zarxio*, a biosimilar to **Amgen Inc.**'s *Neupogen* (filgrastim). On Sept. 14, FDA approved Amgen Inc. and **Allergan PLC**'s *Mvasi* (bevacizumab-awwb), the first biosimilar to **Genentech Inc.**'s *Avastin* (bevacizumab) and the first biosimilar approved in the US for the treatment of cancer.

The agency has 10 biosimilar applications in house, and 27 sponsors have asked for advice on their applications, Gottlieb said. FDA continues to roll out guidance on aspects of biosimilar development, including one on statistical approaches on Sept. 21 *(Also see "Biosimilars Statistical Guidance Reflects Early Development Approach" - Pink Sheet, 21 Sep, 2017.)*

Gottlieb's remarks about reserving market share for biosimilars are noteworthy since they represent a shift in how he has been framing his discussion of drug pricing issues – and even talking about drug pricing much at all is itself a departure for an FDA commissioner.

Having served at the Centers for Medicare and Medicaid services in between his previous stints at FDA and then as a resident fellow at the American Enterprise Institute, Gottlieb is considered a thought leader on drug pricing, but he signaled at his confirmation hearing that he would be sticking to issues under the agency's purview while commissioner. *(Also see "Drug Pricing Pundit Gottlieb Likely To Stay In His Lane At FDA" - Pink Sheet, 14 Apr, 2017.)*

Gottlieb, has, of course, focused on drug pricing since he's come to FDA, but mostly on the supply side – saying that the agency can help with pricing through increasing the number of products available by easing the regulatory burden on approval of generic and innovator drugs. He repeated those themes in other remarks at the Washington Post event.

"One of my concerns is that because development costs are becoming so high and the amount of investment you have to put in is so enormous now, you're seeing fewer and fewer categories where companies want to be the third of fourth to market. In fact, you're seeing oftentimes after the second or third drug comes to market in some of these categories other companies will pull out," Gottlieb said.

> Gottlieb's remarks about reserving market share for biosimilars represent a shift in how he has been framing his discussion of drug pricing issues – and even talking about drug pricing much at all is itself a departure for an FDA commissioner.

Gottlieb added that CAR-T therapy is particularly challenging since it is highly specialized and targeted to fewer than 200 patients per year. FDA approved **Novartis AG**'s *Kymriah* (tisagenlecleucel), the first chimeric antigen receptor T-cell therapy, last month.

Asked if President Trump would be issuing an executive order on drug pricing, as was suggested soon after he took office, Gottlieb replied that he couldn't speak for the White House but that what the agency is doing with respect to drug pricing and drug competition could become a component of any policy the administration puts out. *(Also see "Trump Exec Order On Drug Costs: Seeking To Balance Access, Innovation" - Pink Sheet, 23 Jun, 2017.)*

PRICING DOES NOT CORRELATE WITH DEVELOPMENT COSTS

Gottlieb noted that FDA would be focusing on drug costs and increasing competition at his first address to FDA staff in May. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)* He has expounded on the agency's specific plans in a series of speeches this month.

Following the approval of Kymriah, Gottlieb noted that FDA is developing new policies for preclinical development of products involving new technology platforms, which may require less preclinical data for certain second entry therapies. *(Also see "Gene Therapy Platforms May Require Less Preclinical Data, Gottlieb Says" - Pink Sheet, 7 Sep, 2017.)*

At a subsequent meeting, he announced the agency's plan to reduce drug development costs in the clinical phases, such as by using "seamless trials" that involve one adaptive study where phases receive interim evaluation. *(Also see "FDA's Gottlieb Pushing 'Seamless' Clinical Trials For Faster Development" - Pink Sheet, 11 Sep, 2017.)*

At the Washington Post event, Gottlieb was asked if FDA could do anything to assure that savings from lower drug development costs would be passed on to consumers. He replied that there is not a one-to- one correlation between development costs and pricing.

"People in a competitive market, in a dynamic market, price things to the price they can derive and what they perceive the value to be and what the value is to the end recipient," he said. "Products aren't priced based on some multiple of what it costs to develop them."

Published online September 22, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Pfizer's *Sutent* (sunitinib) for adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy	Oncologic Drugs	Sept. 19
PTC Therapeutics' *Translarna* (ataluren oral suspension) for treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene	Peripheral and Central Nervous System Drugs	Sept. 28
Selection of strains to be included in an influenza virus vaccine for the 2018 southern hemisphere influenza season	Vaccines and Related Biological Products	Oct. 4
Spark Therapeutics' *Luxturna* (voretigene neparvovec) for treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy	Cellular, Tissue, and Gene Therapies	Oct. 12
Aerie Pharmaceuticals' netarsudil ophthalmic solution 0.02% for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Dermatologic and Ophthalmic Drugs	Oct. 13
Clinical development plan for Pfizer's *Staphylococcus aureus* vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations	Vaccines and Related Biological Products	Nov. 7
Discussion of patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. Also discussion of whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions	Bone, Reproductive and Urologic Drugs	Dec. 7

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