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Novartis CAR-T Site Selection, Risk Management Are Model For Other Sponsors

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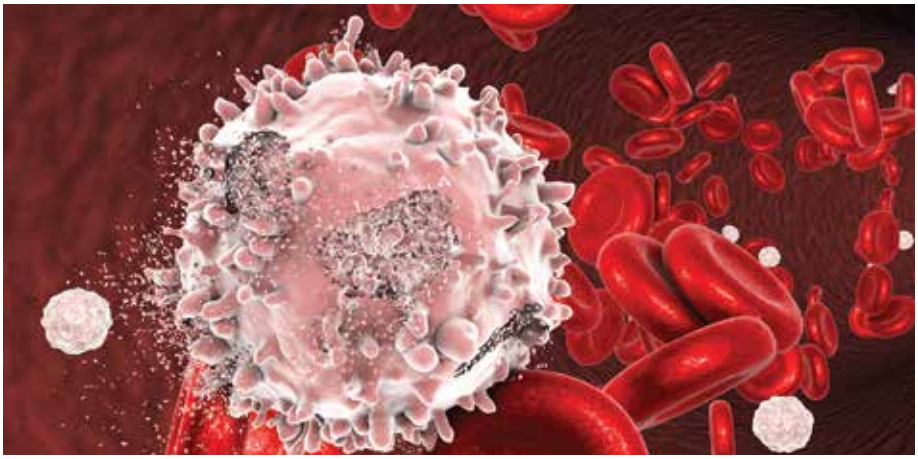

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A US FDA advisory committee's unanimous endorsement of **Novartis AG**'s tisagenlecleucel-T (CTL019) for pediatric leukemia July 12 not only moves the chimeric antigen receptor T-cell therapy closer to commercialization, it provides a benchmark for other CAR-T product developers to follow when it comes to risk mitigation strategies.

All 10 voting members of the Oncologic Drugs Advisory Committee said tisagenlecleucel had a favorable risk/benefit profile for pediatric and young adult patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia (ALL).

> "While I have some concerns about late toxicity, you have to be a long-term survivor to experience late toxicity, and I think that's what this drug gives us." – ODAC Chairman Roth

The efficacy results seen in clinical trials outweighed the serious, but generally manageable, risks of cytokine release syndrome (CRS) and neurotoxicity, panelists said.

Additionally, they were reassured by Novartis' stringent criteria for selecting clinical sites to administer the product and a proposed Risk Evaluation and Mitigation Strategy (REMS) focused, in part, on ensuring that a multi-step algorithm for quickly treating CRS is implemented and followed.

Several committee members viewed tisagenlecleucel as a therapeutic game-changer in the treatment of ALL.

"I think this is the most exciting thing I've seen in my lifetime," said Timothy Cripe, chief of the Division of Hematology/Oncology/Bone Marrow Transplant at Nationwide Children's Hospital.

"This is a very poor risk patient population and this is an unmet need in the pediatric population," said Catherine Bollard, director of the Program for Cell Enhancement and Technologies for Immunotherapy at Children's National Medical Center. "The clinical response was remarkable, and I think Novartis [has] done a great job putting together a plan for mitigating risk going forward."

Panel chairman Bruce Roth, an oncologist at Washington University, said tisagenlecleucel was "clearly a high-risk approach for a disease that has very few alternative options that are also associated with toxicity."

"While I have some concerns about late toxicity, you have to be a long-term survivor to experience late toxicity, and I think that's what this drug gives us," Roth said.

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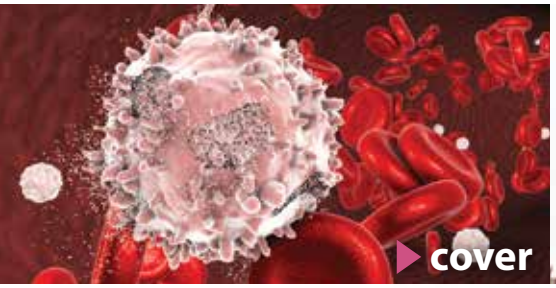
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User Fee Bill Or Drug Pricing Bill? House Members Makes Both Cases

https://pink.pharmamedtechbi.com/PS121090

House passes bill reauthorizing FDA user fee programs via voice vote and makes many other policy changes, but in the process touts the bill's potential to push drug prices lower.

Antibiotic Spring? Regulatory Incentives Spur Activity – And Maybe Medical Advances

https://pink.pharmamedtechbi.com/PS121048

Regulatory incentives have been successful at attracting developers to antibiotic R&D, but significant medical advances have stubbornly remained rare. Now the pipeline has produced the first novel antibiotic to receive breakthrough status from US FDA and some Phase III trials are raising the efficacy bar to superiority.

Spain And Portugal Team Up To Buy Medicines

https://pink.pharmamedtechbi.com/PS121087

Spain and Portugal have announced plans to work more closely together to buy new medicines and are now planning a pilot.

FTC Review Of Colgate Optic White Claims Delays Class Action Complaint

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A Colgate Optic White whitening claims class action complaint is stayed pending an FTC decision on the claims, a federal judge rules. The judge denied the Colgate's motion to dismiss on the grounds the state suit is pre-empted by FDA regulations.

White House Slams Generic Exclusivity Provisions In User Fee Bill

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Trump administration says generic exclusivity provisions – which have been softened from the original bill – are unpredictable and could decrease competition; and while the White House is displeased with exclusivity, and wants higher user fees, it is not explicitly threatening a veto.

Mylan, Amgen Biosimilars Sail Through Advisory Panels, May Diverge From There

https://pink.pharmamedtechbi.com/PS121104

Mylan's Herceptin biosimilar faces questions on off-label use and manufacturing, while Amgen's Avastin biosimilar could be template for other products.

inside:

CONTINUED FROM COVER

The advisory committee recommendation not only appears to put tisagenlecleucel on a path to approval by its Oct. 3 user fee date, it's an early vote of confidence for the many CAR-T therapies currently making their way through development and review.

Kite Pharma Inc.'s axicabtageneto ciloleucel in lymphoma is the next CAR-T product in FDA's regulatory queue, having been filed just about two months after Novartis' agent. *(Also see "Keeping Track: US FDA Approvals Binge Continues With Dupixent, Ocrevus And Zejula; Two CAR-T Are Under Review" - Pink Sheet, 31 Mar, 2017.)*

With the advisory committee now behind it, Novartis's commercial preparations will take on greater focus.

CLINICAL AND PATIENT EXPERIENCE DATA IMPRESS ...

Tisagenlecleucel is a genetically modified autologous immunoceullular therapy in which a patient's own T cells are transduced with a retroviral (HIV-1-based) vector to express a CD19-directed CAR.

In the single-arm pivotal trial, there was an 83% overall response rate in 63 subjects who received a single intravenous infusion of tisagenlecleucel manufactured at Novartis' Morris Plains, N.J., facility. Responses were durable, with a 75% relapse-free rate six months after onset of remission. Overall survival was 89% at six months and 79% at 12 months, Novartis said.

The clinical efficacy data were bolstered at the advisory committee meeting by open public hearing testimony from parents of three children who participated in tisagenlecleucel trials, two of whom are still alive.

... BUT MANUFACTURING CHALLENGES RAISE UNCERTAINTIES

Despite the impressive efficacy data, FDA sought to focus the committee's discussion on product quality and safety issues for the first CAR-T therapy to reach the review stage. *(Also see "Novartis' CAR-T Therapy Faces Quality, Safety Concerns At FDA Advisory Panel" - Pink Sheet, 10 Jul, 2017.)*

"At this time it is still not fully clear how the FDA or Novartis can assure patients that the marketed product would be the same product, particularly with regard to safety and effectiveness, as the product that was studied in clinical trials," said Wilson Bryan, director of the Center for Biologics Evaluation and Research's (CBER) Office of Tissues and Advanced Therapies.

Tisagenlecleucel is the first biologics license application (BLA) to be reviewed through the collaboration of FDA's new Oncology Center for Excellence and CBER. Bryan suggested the advisory committee's review would set the stage for other CAR-T applications to come.

FDA recognizes that there is substantial interest among various stakeholders, including scientists, physicians, patients and their families, in the field of CAR-T products, Bryan said. "What we hear from this committee may be relevant to, and will be considered in, the regulation of other products in this class. However, we ask that the committee focus their deliberations on only tisagenlecleucel and the data in this specific BLA."

ADVISORY COMMITTEE VOTE

Is the benefit/risk profile of tisagenlecleucel favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia? **Y – 10, N - 0**

PRODUCT QUALITY ATTRIBUTES

Novartis representatives explained the product's manufacturing process, as well as steps taken to ensure a rigorous chain of identity and product quality testing to assure consistency and potency.

Novartis expects that upon commercial launch, the turnaround time for manufacturing the product will be 22 days. (*See table.*)

"Novartis has accrued a significant amount of patient-specific manufacturing experience in global multi-center trials, with over 250 batches manufactured to date across various indications," said Spencer Fisk, head of cell and gene technical development at Novartis. "We have established a highly reproducible manufacturing process, with demonstrated manufacturing success. Consistent product safety and quality has been demonstrated by extensive product release and characterization testing."

A representative from **Oxford BioMedica PLC**, which manufactures the lentiviral vector used in the transduction process, also explained steps taken in the vector's design to prevent replication-competent lentivirus and replication-competent retrovirus (RCL/RCR).

Xiaobin Victor Lu, a chemistry, manu-

Tisagenlecleucel Turnaround Time At Launch

ACTIONS	DURATION
Receive leukapheresis material (Day 0)	1 day
Core manufacturing	10-11 days
Testing and disposition	9 days
Pack and ship	1 day
Total throughput time	**22 days**

Source: Novartis slides at July 12 Oncologic Drug Advisory Committee meeting

facturing and controls reviewer in CBER, pointed to lingering product quality and safety uncertainties due, in part, to the heterogeneous nature of the leukapheresis material received from each patient.

"Some product attributes are highly variable from patient to patient and may have limited value for predicting safety and efficacy," Liu said. "Products with variable characteristics were administered in human clinical studies. Vector design has decreased the risk of RCR and insertional mutageneisis. However, insertional mutagenesis cannot be predicted through lot release testing alone."

Advisory committee members said that while RCR was no longer a risk with the current generation of retroviral vectors, insertional mutagenesis could not be ruled out entirely.

Some panelists raised concerns about product potency, particularly with regard the percentage of T cells and CAR-T cells in the final product, suggesting areas for further analysis but nothing that should serve as a barrier to approval.

The panel generally agreed with Novartis' plans for a 15-year observational registry to follow patients who receive commercial product.

LIMITED NUMBER OF CENTERS

The company's criteria for selecting sites that may administer commercial product, and its measures aimed at mitigating the risk of CRS and neurotoxicity, also found favor with the committee.

Novartis is proposing to limit use initially to only 30-35 centers throughout the country that meet Foundation for the Accreditation of Cellular Therapy standards and have experience with T-cell therapies and leukemia. The company will train centers on processes for cell collection, cryopreservation, transport, chain of identity and logistics, and provide educational resources for patients and caregivers, said David Lebwohl, head of the CAR-T franchise global program.

The company also is proposing a REMS aimed at mitigating the risk of CRS and neurological events. The plan is unusual in that its implementation would be a joint responsibility of Novartis and the clinical sites.

"Novartis will be responsible for ensuring an authorized representative is designated at each site," Lebwohl said. "We will provide training for the site personnel on the key adverse events and we will ensure that only certified prescribers can order CTL019."

"The site's designated representative should ensure that all staff complete their training and knowledge assessments and verify availability of anti-cytokine medications," Lebwohl said. "Given the early risk of CRS and the need for early intervention, the site will ensure that patients will stay close to the treatment center for three to four weeks after infusion."

Novartis has developed a CRS management algorithm encompassing five stages of intervention. In light of clinical evidence demonstrating that use of **Genentech Inc.**'s IL-6 inhibitor *Actemra* (tocilizumab) reduces CRS, the drug is recommended as the second-line intervention.

Panelists said the site selection criteria, proposed REMS and CRS management protocol were well thought out.

"Even though cytokine release syndrome sounds really scary, our bone marrow transplant teams are used to dealing with this," Cripe said. "Their mitigation strategies to me are very good and very reassuring."

Very good and very reassured might how industry feels about the entire CAR-T category after the advisory committee.

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NME Mid-Year Report: Approvals Might Near Record With Strong 2nd Half

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After exceeding its 2016 tally of new product approvals by June this year, the Center for Drug Evaluation and Research (CDER) could continue to build off its busy first half and approach record territories for 2017, as another large swath of applications are due for a decision over the next six months.

The US FDA approved **Portola Pharmaceuticals Inc.**'s blood thinner *Bevyxxa* (betrixaban) June 23, bring the novel drug approval total this year to 23, topping 2016's total of 22 less than halfway through the year. *(Also see "Keeping Track: Cardio, Antibiotic Approvals Put FDA Over Last Year's Novel Drug Count" - Pink Sheet, 26 Jun, 2017.)*

There are currently at least 18 new molecular entities (NMEs) and new biological entities (NBEs) awaiting a decision from CDER. (*see chart, p. 6*). If all of the applications are approved without extensions in review times, CDER's new drug approval total would reach 41, just below the totals from 2014 and 2015, years in which the agency set records in its new drug approvals.

One additional product that could be approved in 2017 is **TaiMed Biologics Inc.** and **Theratechnologies Inc.**'s monoclonal antibody ibalizumab designed for the treatment of multidrug-resistant HIV. Ibalizumab has a user fee date of Jan. 3, 2018, but it also has a breakthrough therapy designation, which could prompt FDA to approve it earlier than the goal date.

It is difficult to gauge, however, how many of these applications could result in complete response letters (CRLs). The number of CRLs that CDER issued decreased dramatically in 2010 and stayed

low through 2015. *(Also see "User Fee Extensions Are Key To CDER's First Cycle Review Success" - Pink Sheet, 18 Jan, 2016.)* In 2016, however, the trend came to a halt, as CDER more than a dozen CRLs to NMEs and novel biologic applications. *(Also see "Novel Approvals Were Fewer But Faster At US FDA In 2016" - Pink Sheet, 2 Jan, 2017.)*

So far in 2017, FDA has returned to its low-letter pattern from earlier in the decade. There have only been two announced CRLs from CDER compared with 23 approvals, putting the approval rate at 92%. Even if only half of the announced products in CDER's 2017 pipeline were to gain approval, however, new drug approvals would still total at least 31, a number higher than that of 2011, 2013 and 2016.

Last year's count of 22 novel approvals was the lowest annual total for the center since 2010. While a high number of CRLs was certainly a factor, former Office of New Drugs Director John Jenkins had noted that CDER received fewer than the average number of novel applications to review for that year. *(Also see "Do FDA Submission, Approval Declines Outside Cancer Signal Future Treatment Gaps?" - Pink Sheet, 14 Dec, 2016.)*

AN INNOVATIVE FIRST HALF TO BOOT

On top of CDER's torrid pace of new drug approvals in the first half of 2017, many of the approved products demonstrated a high level of innovation.

More than half – 14 – of the 23 approvals were awarded priority review. Additionally, 10 of the approved products picked up a breakthrough therapy designation along the way.

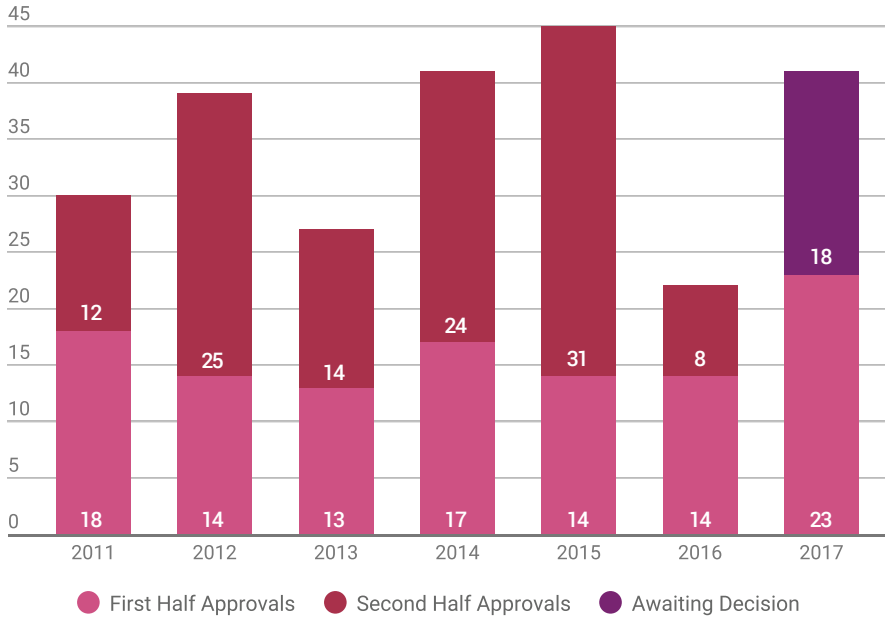
Breakthrough therapy designations are a lot of work for FDA, but also an effort that agency believes its critical to its mission. In May 2017, there were eight breakthrough therapy designations announced, which appears to be the most in any month since the agency started granting them in 2013. *(Also see "US FDA's Record-Breaking Month Of Breakthrough Therapy Designations" - Pink Sheet, 1 Jun, 2017.)*

The second half of 2017, however, will almost certainly see fewer approved products with breakthrough therapy designations. Only three products in CDER's 2017 pipeline, not counting Ibalizumab, landed a designation. These include **AbbVie Inc.**'s glecaprevir and pibrentasvir compound for the treatment of chronic hepatitis C, **Gilead Sciences Inc.**'s fixed-dose combination hepatitis C treatment of sofosbuvir, velpatasvir and voxilaprevir, and **Pfizer Inc.**'s inotuzumab ozogamicin for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

Priority reviews, however, will remain prominent over the next six months, as 10 of the 18 products are slated to get the expedited review clock.

Published online July 12, 2017

CDER Approvals By Year



CDER's 2017 Pipeline

PRODUCT	SPONSOR	GOAL DATE	INDICATION
UX003 (recombinant human beta-glucuronidase)	Ultragenyx Pharmaceutical	Nov. 16, 2017	Sly Syndrome
Copanlisib	Bayer	Oct. 17, 2017 or earlier	Relapsed or refractory follicular lymphoma
Vyzulta (latanoprostene bunod)	Valeant	Aug. 24, 2017	Open angle glaucoma or ocular hypertension

PRODUCT	SPONSOR	GOAL DATE	INDICATION
Ertugliflozin Ertugliflozin and sitagliptin Ertugliflozin and metformin	Merck and Pfizer	December 2017	Type 2 diabetes
Translarna (ataluren)	PTC Therapeutics	Oct. 25, 2017	Nonsense mutation Duchenne muscular dystrophy
Semaglutide	Novo Nordisk	Dec. 5, 2017 or earlier	Type 2 diabetes
Tremfya (guselkumab)	Janssen	July 17, 2017	Moderate to severe plaque psoriasis
Benralizumab	AstraZeneca	October 2017 to December 2017	Severe, uncontrolled asthma in patients with an eosinophilic phenotype
Sirukumab	GlaxoSmithKline and Janssen Biotech	Sept. 23, 2017 or earlier	Moderately to severely active rheumatoid arthritis who have failed or are intolerant to one or more disease-modifying anti-rheumatic drugs
Solosec (secnidazole)	Symbiomix Therapeutics	Sept. 17, 2017	Bacterial vaginosis
Glecaprevir and pibrentasvir	AbbVie	Aug. 19, 2017 or earlier	Chronic hepatitis C virus genotype 1 to 6 infection
Sofosbuvir, velpatasvir, and voxilaprevir	Gilead Sciences	Aug. 8, 2017	Direct-acting antiviral-experienced patients with hepatitis C virus genotype 1 to 6 infection without cirrhosis or with compensated cirrhosis
Inotuzumab ozogamicin	Pfizer	August 2017	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia
Meropenem-vaborbactam	The Medicines Company	August 2017	Complicated urinary tract infections
Idhifa (enasidenib)	Celgene and Agios	Aug. 30, 2017	Relapsed or refractory acute myeloid leukemia patients with an IDH2 mutation
Nerlynx (neratinib)	Puma Biotechnology	July 21, 2017 or earlier	Early stage HER2-overexpressed or amplified breast cancer who have received prior adjuvant therapy based on trastuzumab (Roche's Herceptin)
Evenity (romosozumab)	Amgen and UCB	July 19, 2017	Osteoporosis in postmenopausal women at increased risk of fracture
Ozenoxacin	Medimetriks Pharmaceuticals and Ferrer	June 27, 2017	Impetigo in adults and pediatric patients aged 2 months and older
Ibalizumab	TaiMed Biologics and Theratechnologies	Jan. 3, 2018	Multidrug resistant HIV-1 infection

ANDA Approvals Break Record, May Set New Normal

DERRICK GINGERY derrick.gingery@informa.com

FDA's most recent ANDA approval total set a record and may represent a new productivity standard.

The agency's Office of Generic Drugs reported approving 88 applications in June, a new record monthly total by a wide margin. It is the first time more than 80 ANDAs have been approved in a single month since the generic drug user fee program launched in October 2012.

The total came after 77 approvals were posted in May, which at the time was the highest total in fiscal year 2017 and the second-highest monthly total of the GDUFA era.

The previous monthly record was 79 approvals, reported in December 2015. (*See charts.*)

The monthly performance figures may signal a new output level for FDA's generic drug review staff.

FDA told the Pink Sheet that many factors affect monthly approval totals, but steadily increasing approval figures are not new and that the agency can still improve its productivity.

"The agency is building up to its GDUFA stride," FDA said July 10 in an emailed statement.

OGD now has approved more than 60 ANDAs in four of the last five months and is averaging more than 62 approvals per month for the fiscal year. The agency averaged about 54 approvals per month in FY 2016 and 41 per month in FY 2015.

FDA is on pace to approve 753 ANDAs in FY 2017, which would be 100 more than the record annual total set in FY 2016.

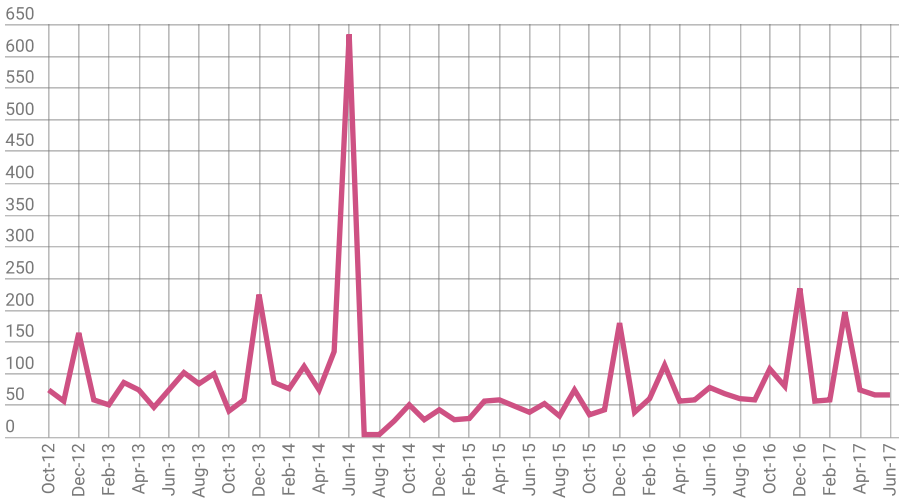
As more reviewers and other staff are hired and trained, OGD's productivity level can move higher. The agency hired more than 1,500 new employees related to GDUFA through the end of FY 2016. The agency also cut its first-cycle review time substantially during the program's first three years. *(Also see "Generic Drugs: First-Cycle Review Times Improve, But Hundreds Of ANDAs Still Pending" - Pink Sheet, 4 Jul, 2017.)*

Robert Pollock, senior advisor and outside director to the board at Lachman Consultants, told the Pink Sheet that "increased communication and responsiveness" from the Office of Compliance and others in addition to OGD have helped productivity. Pollock predicted that the approval figures will remain at these levels going forward.

The agency made a similar productivity jump in FY 2015. Up to that point, the agency had posted more than 45 approvals in a single month only once. Beginning in April 2015, the agency began reporting consistently higher totals, including 50 and 60 approvals per month, through the rest of FY 2015 and FY 2016. *(Also see "ANDA Approvals, Complete Responses Hit Record In FY 2016" - Pink Sheet, 12 Oct, 2016.)*

However, the approval increase in FY 2017 still likely will be dwarfed by the total number of submissions received. In-

ANDA Submissions Remain Low...



...But Approvals Jump To New Record

FDA's Office of Generic Drugs posted a new record number of approvals in June after a near record in May, while submissions remained down following a spike in March.

Source: FDA generic drug program activity report

dustry has argued the agency must average more than 100 approvals per month to deal with the applications being submitted. *(Also see "ANDA Approvals Soar, But Does FDA Need To Do More?" - Pink Sheet, 16 May, 2016.)*

WAS AGENCY GENERIC PRIORITIZATION PLAN FACTORED IN?

FDA's encouraging approval totals also arrived just after the agency announced its plan to streamline generic reviews in the hopes of pushing prices down.

Commissioner Scott Gottlieb said June 27 that internal policy had been updated to increase the number of ANDAs that could be prioritized to include reference products with fewer than three approved generics. *(Also see "FDA Drug Pricing Policy Offers Short-Term PR Gain, More Long-Term Actual Benefit" - Pink Sheet, 27 Jun, 2017.)*

In addition, the agency published a list of 267 drugs that were off-patent and had no remaining exclusivity, but no generic competition, to encourage development in those markets. *(Also see "Generic Industry Gets 267 Reasons From FDA To Pursue ANDA Development" - Pink Sheet, 27 Jun, 2017.)*

The agency in its statement to the Pink Sheet added that with its "record number of approvals in June, we continue to improve patient access to affordable drugs."

There is no evidence that the monthly approval record is related to the policy announcement, but it may give sponsors more confidence that their applications can be approved quickly if they decide to pursue applications on the list.

Increased approval speed will depend in part on submission quality. The agency would prefer most ANDAs require two review cycles instead of three or more. *(Also see "ANDA Reviews: First-Cycle Desired, But Two-Cycles OK?" - Pink Sheet, 27 Jul, 2015.)*

SUBMISSIONS REMAIN IN POST-BOLUS LOW

Equally good news about ANDA submissions arrived with the new approval totals.

FDA received 66 submissions in May and 67 in June, both well below the monthly average for the fiscal year. It is the third straight month with low submission totals following a bolus in March. The rush was attributed in part to generic companies in India working to close out their portfolios at the end of their calendar year. *(Also see "ANDA Submissions Continue Yo-Yo Pattern, Unlike Approvals" - Pink Sheet, 10 May, 2017.)*

Since the March bolus, the agency has seen the potential annual ANDA total (based on the monthly average) drop from 1,472 to 1,259.

The reduction in submissions could be partially explained by the March rush as ANDAs that normally would have been submitted over several months were sent at one time.

After the most famous ANDA rush in June 2014, when sponsors tried to avoid new stability requirements, FDA saw a similar pattern. *(Also see "ANDA Lull Begins: OGD Receives Four Applications In July" - Pink Sheet, 25 Aug, 2014.)*

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EMA Brings Non-EU Regulators Into CHMP Meetings

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Israeli regulators took part as observers in a CHMP meeting, according to the agency's 2016 activity report. The move was part of a wider EMA initiative to increase the involvement of non-EU regulators in EMA scientific reviews and to improve work sharing.

According to its report on activities in 2016, the EMA shared an assessment report for a centralized product with Israeli regulators who then took part as observers in the May meeting last year during discussion on the list of questions. The regulators were also invited to join Day 120 discussions for the product in November.

The CHMP's 2017 work plan, adopted in February, includes a key objective to "explore mechanisms to enhance involvement and strengthen liaison with non-EU regulators in EMA scientific reviews, in order to facilitate work-sharing and promote capacity building."

The same plan also calls for CHMP involvement in improving the perception and use of the so-called Article 58 procedure, which allows the EMA to issue positive recommendations on new medicines intended for use in non-EU markets. The EMA has been keen to promote the use of Article 58, especially in Africa. *(Also see "EMA Review Of Non-EU Drugs To Be Made More Useful For African Regulators" - Pink Sheet, 21 Feb, 2017.)(Also see "Could The EMA Be A Regulatory Model For East Africa?" - Pink Sheet, 26 May, 2017.)*

Meanwhile, the EMA also wants to increase the participation of patients in CHMP meetings following a successful pilot earlier this year. *(Also see "Pharma Firms Told To 'Keep Your Distance' When Patients Come To EU CHMP Meetings" - Pink Sheet, 9 May, 2017.)*

From the editors of Scrip Regulatory Affairs. Published online July 7, 2017

EMA Suspends Some Activities To Focus On Brexit Relocation

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Shutterstock: Gordon Bell

> "More resources may need to be diverted from other activities planned in 2018 into core activities that need to be maintained" – EMA spokesperson

The European Medicines Agency says that it is putting certain lower-priority activities on hold and may need to divert resources away from activities planned for 2018 so that it can prepare for its Brexit-related relocation and focus on its core tasks.

Keeping its operations running smoothly and retaining as many staff as possible during the move is a key priority for the EMA, not to mention stakeholders like the life sciences industry, which fear that otherwise the agency's functioning could be impaired and public health put at risk. Concern has been expressed that the agency could lose up to 50% of its staff as a result of the move, with its future location expected to be a key factor in terms of staff retention.

The issue has been raised on numerous occasions, including at the Drug Information Association's EuroMeeting in April this year, where the EMA's Melanie Carr said the agency has been planning various scenarios based on relocation preparedness, operational and financial preparedness, human resource matters, and communications. *(Also see "Brexit: Scenario Planning Well Under Way At EMA" - , 7 Apr, 2017.)* More recently, European drug industry federation EFPIA specifically called for measures to be taken to ensure continuity of the agency's work. *(Also see "EFPIA Calls For Interim Accords To Ease Brexit Impact" - Pink Sheet, 23 Jun, 2017.)*

In order to deal with the potential staffing and other issues, the EMA has drawn up a business continuity plan on Brexit preparedness, which it presented to its management board in June. The EMA said the board "endorsed the principles and the methodology that will help EMA prioritise its activities to make available the necessary resources to prepare for Brexit and cope with a potentially significant staff loss."

Details of the plan have not yet been made public, but an EMA spokesperson told the *Pink Sheet* that the prioritization outlined in the plan would allow the agency to allocate freed-up resources to core activities. "This will ensure that the Agency will always be able to fulfil its core tasks."

The plan allows the agency to address two situations that may arise, the spokesperson said:

- The need to ensure the necessary human resources are available to work on Brexit preparedness.
- Potential staff losses that cannot be compensated through the recruitment of replacement resources.

Some activities that were assigned a lower priority have already been suspended or postponed to allow the agency to prepare for the relocation and for "the necessary changes of business procedures and operations," according to the spokesperson.

To deal with additional staff losses, "more resources may need to be diverted from other activities planned in 2018 into core activities that need to be maintained under any circumstance."

The agency has set up two working groups to look at how best to allocate the additional regulatory workload if the UK Medicines and Healthcare products Regulatory Agency is no longer part of the network after Brexit. *(Also see "Pharma Execs Urge Post-Brexit Regulatory Deal, As EMA Focuses On Redistribution Of MHRA Work" - Pink Sheet, 7 Jul, 2017.)* The groups met on July 5, the EMA said, adding that more information on these activities will be published in the next few weeks.

The EU has listed six "objective" criteria that the agency's new host city must meet, including connectivity and access to education facilities for agency staff. More than 20 countries are expected to put in bids by the July 31 deadline.

From the editors of Scrip Regulatory Affairs. Published online July 11, 2017

We'll See You In Court: UK Pharma Challenges Extra NHS Price Hurdle

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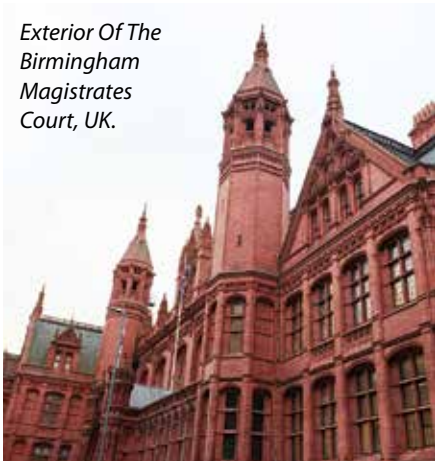
The Association of the British Pharmaceutical Industry has confirmed a report in the Financial Times newspaper that it has applied for a judicial review over the introduction by the National Institute for Health and Care Excellence (NICE) in April of an additional negotiation process known as a budget impact test. This test involves an evaluation of medicines that have already been assessed as cost-effective but are likely to cost the National Health Service more than £20m in any of the first three years of use.

Presently, NHS England has had to allow patients access to a drug within 90 days of a NICE recommendation but the budget impact test means the former is granted more time to negotiate with pharmaceutical companies over price, up to a maximum of three years. The ABPI, noting that NICE's own analysis shows that around one in five new medicines will be impacted, says the new procedures "have the potential to cause significant delays for patients waiting for treatment for a range of conditions, including for cancer, heart disease and diabetes".

BUDGET IMPACT TEST 'CREATES UNCERTAINTY'

Clearly, the ABPI has had enough, saying "it is important to challenge these new procedures before the first medicines get caught in the system, creating uncertainty for patients about whether they will be able to receive them". The association concluded by saying it is now "reluctantly seeking to challenge the NICE decisions".

ABPI chief executive Mike Thompson said that "after many months of raising concerns with NICE, NHS England and the Department of Health and offering to work constructively on alternative proposals, we have applied to formally challenge these proposals in court. We believe this to be the right course of action due to the potential damage these changes will cause to NHS care and on our ability to research, develop and use new medicines here in the UK. We hope that the Government will reverse the changes and work with us to find a solution that works for everyone".



Exterior Of The Birmingham Magistrates Court, UK.

Shutterstock: Monkey Business Images

However, Thompson's stance is not entirely backed by his counterpart at the BioIndustry Association, Steve Bates. In an email to the *Pink Sheet*, he said: "The BIA is not party to this process nor have we been consulted upon it. As such it would be inappropriate to comment on the specifics of this action at this stage."

BIA FOCUSED ON OTHER 'COMPLEX ISSUES'

Bates added that ensuring NHS patients continue to have access to innovative medicines and treatments "is clearly an important objective. However, there are currently several other complex issues the full life sciences sector is currently engaging with the government on. Namely, how we can make Brexit a success for the life sciences sector and how we can develop the most impactful industrial strategy to support the BIA's ambition that the UK sustains itself [as] a leading global cluster for life sciences."

Bates ended by saying "this legal move must not impact or delay broader industry engagement with the UK government at a time of significant external change."

There was more sympathy for the ABPI's position from patient groups. Baroness Delyth Morgan, chief executive at Breast Cancer Now, said: "We remain extremely concerned that the budget impact test could see NHS patients experience delays in accessing vital and cost-effective drugs. From the outset, it was incredibly disappointing that, despite widespread opposition from those representing patients and a willingness to discuss alternative solutions, NICE and NHS England decided to implement this test."

TEST REPRESENTS MAJOR ADDITIONAL HURDLE

She added that "getting modern breast cancer drugs through to the NHS patients that desperately need them is already very difficult and this test could represent a major additional hurdle. Thousands of women living with incurable breast cancer are relying on effective drugs to give them significant and precious extra time with their loved ones, and any further delays could sadly see patients lose their lives as they wait."

Morgan ended by saying: "We will now be monitoring the progress of this possible legal action closely, and hope that it will provide clarity on the issue of timely access to drugs in England. We, alongside many other charities, remain ready and willing to work with all involved to look at how this critical issue can be resolved."

As for NHS England and NICE, they remained tight-lipped when contacted by the *Pink Sheet*, saying they have no comment at this time. There is no great hurry given that it is likely to be a few months before the courts will decide on whether a review will be undertaken.

From the editors of Scrip Regulatory Affairs. Published online July 13, 2017

FDA Inspection Yields Insight Into Biocon/Mylan Biosimilars Manufacturing Challenges

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A US FDA preapproval inspection raises more questions about the readiness of the Biocon Ltd. biosimilars manufacturing facility in India that European authorities have found to be non-compliant with EU GMP requirements.

An FDA team issued a Form 483 report of inspectional observations made at the facility on April 7, just three weeks after France's inspectorate visited the site, which Biocon and partner Mylan have tapped for production of biosimilars.

The French National Agency for Medicines and Health Products concluded based on its March 13-17 inspection that the plant in Bangalore, India, failed to comply with EU GMP requirements.

Until the non-compliance notice is lifted, the French authority urges the European Medicines Agency not to approve EU marketing authorization applications for three biosimilars Mylan and Biocon intend to manufacture there, pegfilgrastim (*Fulphila*), trastuzumab (*Ogivri*) and insulin glargine (*Semglee*). *(Also see "Will GMP Lapses Stall Biocon-Mylan's Biosimilars Build-Up?" - Scrip, 11 Jul, 2017.)*

NOT READY FOR PRIME TIME

Mylan/Biocon have biosimilar applications pending at FDA for US versions of two of the biosimilars on hold in the EU, trastuzumab (*Herceptin*) and pegfilgrastim (*Neulasta*).

With user fee goal dates of Sept. 3 for trastuzumab and Oct. 9 for pegfilgrastim, Biocon will have to work quickly if it is to resolve FDA's concerns about its manufacturing operation before the agency decides on approval. Mylan had appeared on track for a smooth advisory committee review of the trastuzumab biosimilar on July 13 before the manufacturing problems surfaced.

In response to media reports regarding the 483 report, Biocon said May 5 that the company "has already responded to US FDA on all observations of the recent audit within stipulated timelines."

Aerial view of Biocon Park

"With user fee goal dates of Sept. 3 for trastuzumab and Oct. 9 for pegfilgrastim, Biocon will have to work quickly if it is to resolve FDA's concerns about its manufacturing operation before the agency decides on approval.

A Mylan spokesperson told the Pink Sheet on July 11 that the company already has responded to FDA's observations and that "we remain confident in Biocon's capabilities from both a development and manufacturing perspective." Mylan has an exclusive partnership with Biocon for global development, manufacturing, supply and commercialization of a portfolio of biosimilar and insulin products.

A redacted version of the Form 483 report that FDA's Center for Drug Evaluation and Research subsequently posted to its electronic reading room provides more insight into the facility's issues than does the EU non-compliance notice. On the whole, the FDA report gives the impression of an operation that is not quite ready for prime time, but could be if its procedures were tightened up.

The EU notice said the French inspection identified 35 deficiencies. None were critical but they included major deficiencies in these 11 areas: environmental monitoring, training, out-of-specification results management, cleaning validation, process validation, vendor qualification, media fill test, cross-contamination risks, batch manufacturing record, differential pressure alarms management in classified areas, and enterprise software access management for batch certification.

The FDA Form 483 report, the result of a March 27 to April 7 inspection by a team of eight, including seven who hold doctorates, provided a more detailed critique than did the French inspection, focusing mainly on batch records and OOS results management.

DETAILS OF FDA TEAM'S FINDINGS

There were discrepancies between the manufacturing process FDA's team observed and the one described in application documents in terms of in-process specifications, bulk storage conditions and acceptance criteria.

Several factors defined as drug substance acceptance criteria in application

Photo courtesy of Biocon

documents are treated differently in the batch manufacturing record. For example, in two cases, if the criteria aren't met, operators are instructed to "take a deviation and continue." In a third case, various chromatography acceptance ranges are treated as limits in the batch record.

There were problems with the batch release procedures the quality assurance unit had approved and implemented. The procedures allowed the release of drug product even if the drug substance was out of specification or had open deviations. They also allowed laboratory analysts to release the raw material batches that they themselves had tested.

There were issues with the drug substance and drug product quality control testing procedures that reflected a lack of quality oversight. For example, bioburden testing procedures lacked important details. Also, the instructions for acting on in-process testing results weren't enough to ensure adequate processing of drug product.

Furthermore, FDA said there's no assurance that the methods for drug substance and drug product release testing can be suitably performed in the QC laboratories or that the methods will remain in a validated state. There is a lack of instruction on when to resort to manual integration of chromatography data and how to perform it. Testing protocols fail to say how new or atypical peaks would be addressed. Laboratories would be allowed to stray from validated methods by substituting reagents, consumables and equipment that they deemed equivalent. Also, host-cell protein testing instructions were unclear.

The procedure for dealing with out-of-specification test results is "internally inconsistent and not clear."

Without proper justification, deviations were not opened or closed in time. In one case, the reason given was "prioritization of other activities;" in another, it was "discussion between cross-functional team."

Going forward, activity priorities and team discussions are likely to focus more on resolving the concerns that the US and EU authorities have raised.

From the editors of the Gold Sheet.
Published online July 11, 2017

Physician Inducements: Bring On The Sunshine (Act) Say Indian Firms

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Indian drug firms appear keen to support the introduction of stricter rules on the payments they make to physicians and say that they are open to making disclosures along the lines stipulated in the US Physician Payments Sunshine Act.

"We have proposed making disclosures of such payments similar to the Sunshine Act of the US," Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents leading domestic firms, told the Pink Sheet.

Read the full article here

Firms could be asked to mandatorily make disclosures within 90-days of such payments, with "severe" penalties for non-disclosure, Shah suggested.

The Indian industry's seeming efforts towards openness on physician payments comes in the backdrop of the government's plans to regulate unethical practices in the pharmaceutical and healthcare sector, via a more effective uniform code for pharmaceuticals marketing practices (UCPMP). Physicians are separately also under fire in India over the so called "cut -practice" within the medical profession.

Inducements from pharma to physicians in the past have ranged from giving gifts, "developing" doctor's clinics and sponsoring the higher education of children of influential physicians to cruise tickets and conferences in exotic locales, though the UCPMP attempted to curb some of these, albeit via a voluntary approach. Last year, US multinational Abbott was under fire in India for allegedly using medical "camps" [in some cases the firm's sales personnel apparently doubled up as the test technicians] and a questionable "survey" approach to bolster prescriptions for a diabetic neuropathy drug – charges that it has strongly denied. *(Also see "Abbott's Medical Camps In India: Genuine Effort or Proxy Sales Plan?" - Scrip, 28 Dec, 2016.)*

IPA's Shah believes that Sunshine Act-style rules could address "a major chunk of the problem" in India and says it is perhaps a "more practical approach". In addition, when such data is in public domain, it would also perhaps put pressure on erring physicians to stay clean.

SUNSHINE ACT REQUIREMENTS

It is not clear if the Indian government intends, at this stage, to consider industry's suggestion. Sunshine-type rules would perhaps require fresh laws via India's health ministry.

The US Sunshine Act is intended to make relationships between industry, including device firms, and healthcare providers transparent and typically requires applicable companies to report payments and other "transfers of value" provided to physicians and teaching hospitals to the Centers for Medicare and Medicaid Services (CMS). Physicians and teaching hospitals are, though, given an opportunity to review and dispute such reported payments. In 2016, medical product manufacturers reported $8.1bn in payments and ownership and investment interests to physicians and teaching hospitals under the CMS' Open Payments program.

Last year, senior government functionaries indicated that India's UCPMP, so far voluntary in nature, may be on course to becoming "statutory" and "mandatory" – the code had apparently been referred to India's law ministry, though there is no official confirmation on this.

Last year, senior government staff indicated that India's now voluntary pharmaceutical marketing code may be on course to becoming "statutory" and "mandatory," though there is no official confirmation on this.

PHYSICIAN CUT PRACTICE

While action is awaited on the UCPMP and industry's suggestions around the Sunshine Act, more pressure appears to be piling on physicians from other quarters as well. This, with specific reference to the rampant "cut-practice" in the medical profession.

Such cuts essentially entail a referring doctor getting paid by the specialist consultant physician or diagnostic center/lab for patient referrals – such kickbacks pile up substantial costs on patients in a largely self-pay market like India. While the pharmaceutical and device industry may not have a direct role in physician cuts, there are probably trickle-down benefits in some cases especially when unnecessary tests and procedures are recommended for patients.

The controversy over physician cuts has now reached a crescendo of sorts with the Western state of Maharashtra, of which Mumbai is the capital, now mulling tough measures against such practices – it may cover hospitals and nursing homes too. The state government is reported to have appointed a committee led by a former director general of police, Pravin Dixit, to study regulations against cut practices and kickbacks in developed nations like the US ahead of framing guidelines on the issue. The panel has had initial meetings, with another expected later this month.

The potential law is expected to make the cut-practice a cognizable offence, with offenders facing punitive action and possibly even jail terms, though the Pink Sheet could not immediately verify the specifics.

A leading physician, who preferred not to be identified, told the Pink Sheet that it was high time that the cut-practice was curbed and suggested "deterrent" punishment.

"Don't know if we want to fill up jails like the US. Take away [the physician's] license to practice for six months," he added.

Industry veteran Ajit Dangi, president and CEO of Danssen Consulting and a former director general of the Organization of Pharmaceutical Producers of India, believes that the voluntary code of conduct for medical professionals as well as for pharmaceutical companies is a "failed model" not only in India but across the world. Virtually every large pharma company in US has been fined for unethical practices and the fine often runs into billions of dollars, he noted.

"We need the US-type of model not only in a state but nation-wide, where the erring party once proven guilty is punished by jail term. Even in an advanced economy like the US, the government is unable to break the nexus between pharma companies, insurance firms and physicians," Dangi, a former president and executive director of **Johnson & Johnson** in India, told the Pink Sheet.

CUT PRACTICE HERE TO STAY?

Dangi believes that the root cause of lack of ethics in the medical profession is proliferation of "donation" doctors – an estimated 50% of doctors in India have graduated by paying cash donations to the private colleges for their education. Many of these colleges are run by politicians, he says.

"The first goal of such 'donation' doctors when they start practicing is 'return on investment'. This results in the cut practice, tie ups with pharmaceutical companies for generating maximum number of prescriptions, commission from pathology/diagnostic labs as well as from senior consultants for referrals etc," Dangi claimed.

The cut-practice and its linkage to India's medical education "enterprise" has been denounced in the past too. An article in the Indian Journal of Medical Ethics in 1996 noted how the medical profession itself has "nurtured" the cut-practice. Author, PA Kale, then noted how the indiscriminate proliferation of medical colleges with "open and shameless support of those in power" was adding hundreds of inadequately trained medical graduates every year to the pool of practicing doctors. A large majority of these, Kale said, are concentrated in urban areas "with attendant intense competition and battle for survival which favor cut practice".

"Pernicious as it is, cut practice has come to stay," Kale, then professor of cardiology, Seth CS Medical College and KEM Hospital, Mumbai, noted in the article.

AKIN TO CARTELS?

Some industry experts suggest that the concept of providing a "commission" for service isn't unhealthy because it is legally practiced across various industries and an efficient way in which a buyer and seller are brought together for economic activity. The problem though, a senior official from a leading pharmaceutical firm told the Pink Sheet, is when this is done "purely for gain" and such activity is "akin to cartels" and must not be allowed.

"Obviously making information easily accessible to people is the best solution, since it allows them to make informed choices. But politically, it is always more profitable to bring in regulations – however draconian," the official added.

Currently, under the Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations a physician is not permitted to "give or offer to give, solicit, or receive any gift, gratuity, commission or bonus" in consideration of or return for "referring, recommending or procuring" any patient for medical, surgical or other treatment. "A physician shall not directly or indirectly, participate in or be a party to act

of division, transference, assignment, subordination, rebating, splitting or refunding of any fee for medical, surgical or other treatment," these regulations add.

But industry experts say that such regulations are flouted with ease, rarely evoking prompt action by the medical council – it usually serves "everyone's interest" to look the other way, they maintained. Previous government data indicated that in 2011-12 the Medical Council of India (MCI) received 561 complaints against violation of the code of ethics of doctors. In 2012-13, this figure stood at 623 while it dropped to 234 in 2013-14. Of the cases disposed of, registration was "temporarily removed" in just three cases in 2011-12, 52 (2012-13) and six (2013-14), a government statement in 2014 said.

BILLBOARD CAMPAIGN

Interestingly, the Maharashtra state's proposed clamp down against cuts follows a controversial billboard campaign by the Asian Heart Institute (AHI) in Mumbai led by prominent cardiac surgeon Ramakanta Panda. One such hoarding by the hospital in the city read: "Honest opinion, no commission to doctors". Last month the AHI had written to the Maharashtra Medical Council seeking action against the cut-practice.

Panda, who is vice chairman and managing director at AHI and the hospital's chief consultant for cardiovascular thoracic surgery, believes that medical treatment costs can by pruned substantially if the cut-practice is done away with.

While the AHI's campaign exposed the fissures within the medical community on the issue, it was criticized by no less that the Indian Medical Association (IMA), which local reports say went on to complain to the Advertising Standards Council of India.

ZERO TOLERANCE

Krishan Kumar Aggarwal, national president of the IMA, in a recent blog, said that the IMA will have "zero tolerance" for unethical practices by medical professionals and medical establishments.

"These include referral fee, cuts, commissions received 'without involving any services'. Offenders can get their names removed from the primary membership of IMA," Aggarwal said in a post, dated July 4. He also noted that the IMA "will not tolerate" any targets given to medical specialists who join hospitals. "IMA will soon come out with a standard appointment contract between consultant and corporate hospitals."

The cut-practice in India made the headlines some years ago, when HS Bawaskar, a physician from Mahad in Maharashtra, filed a complaint with the state medical council after he received a cheque payment for "professional services" from a well know diagnostic chain for referring a patient to it.

From the editors of PharmAsia News.
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FDA's NDA And BLA Approvals: Endari, Tremfya

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				
Emmaus	*Endari* (L-glutamine)	5 g oral powder to reduce the acute complications of sickle cell disease in adult and pediatric patients five years of age and older. *(Also see "Keeping Track: US FDA Approves Sickle Cell Therapy Endari; Array Submits Binimetinib Again" - Pink Sheet, 10 Jul, 2017.)*	S, 5	7/7/2017
New Biologics				
Janssen Biotech	*Tremfya* (guselkumab)	Interleukin-23 blocker to treat adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.		7/13/2017

KEY TO ABBREVIATIONS	
Review Classifications	**NDA Chemical Types**
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

FDA's 21st Century Cures Plan Gives Patient-Focused Drug Development A Boost

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FDA's plan for issuing the patient-focused drug development guidance documents required under the 21st Century Cures Act includes numerous public workshops and a slightly more aggressive timeframe for some draft guidances than required under the pending agreement to reauthorize the Prescription Drug User Fee Act (PDUFA VI).

In total, the schedule FDA lays out in its "Plan for Issuance of Patient-Focused Drug Development Guidance Under 21st Century Cures Act" calls for five public workshops through December 2019 and seven draft guidances through June 2020, with target dates for final versions of the documents stretching out to December 2021.

The guidance plan was highlighted in a July 7 blog post by Commissioner Scott Gottlieb announcing release of FDA's final work plan, proposed funding allocations and list of deliverables under the Cures legislation, which was enacted in December.

The guidance development plan was put together by the Center for Drug Evaluation and Research working in conjunction with the Center for Biologics Evaluation and Research. The workshops and new guidance documents encompassed in the document "will set forth our plan to facilitate a more systematic approach to gathering and using patient perspectives to inform FDA's regulatory decision-making," Gottlieb said.

PDUFA VI GUIDANCES PICK UP PACE IN 'CURES' PLAN ...

The Cures legislation contains several measures aimed at emphasizing and increasing the role of the patient voice in drug development and review. For example, FDA must make public a brief statement about whether and how patient experience data and related information were used in the review of a drug or biologic application. *(Also see "21st Century Cures Revisions Tell FDA To Highlight 'Patient Experience Data'" - Pink Sheet, 27 Nov, 2016.)* The agency also must issue periodic reports on the use of patient experience data in regulatory decision-making.

Section 3002 of Cures requires FDA to issue "one or more guidance documents, over a period of five years, regarding the collection of patient experience data, and the use of such data and related information in drug development."

The guidance documents are intended to bridge from the 22 disease-area meetings taking place under PDUFA V to methodologically sound, fit-for-purpose tools to systematically collect important information about patients' experiences, including burden of disease, and treatment burden and benefit.

In Cures, Congress described the subject matter to be addressed through guidance documents and said that least one draft guidance should be issued within 18 months of the law's enactment, with a revised draft or final guidance due not later than 18 months after comment period closes.

Nevertheless, the statute largely left the timing of the guidance documents' development, and their format, to the agency's discretion, likely because FDA had already committed to develop several of the documents under the PDUFA VI agreement that predated the final version of the Cures legislation.

Of the seven patient-focused drug development guidance documents FDA plans to develop under Cures, four are also explicitly required under the PDUVA VI agreement. *(See chart)* In addition, the PDUFA VI agreement letter includes a commitment by FDA to conduct public workshops to gather input ahead of each draft guidance's release.

The Cures guidance development plan accelerates the target date for each of the four draft guidance documents required under PDUFA VI. The PDUFA VI target dates were at the end of each fiscal year (Sept. 30) from 2018 to 2021. In contrast, the Cures plan moves those target dates up by three months to June in each of the four years.

The agency also appears to have blended one Cures requirement with a PDUFA VI guidance commitment.

Cures requires FDA to issue guidance on how the agency anticipates using relevant patient experience data to inform regulatory decision-making. FDA said it will integrate this information into its benefit-risk assessment framework as part of a draft guidance on benefit-risk assessments.

The benefit-risk assessment framework guidance was required under the PDUFA VI agreement by September 2021; under the Cures plan, the draft is targeted for release by June 2020.

... BUT USER FEES WILL PAY MOST OF THE COST

Given the substantial overlap in patient-focused drug development guidance requirements between PDUFA VI and Cures, most of the funding for the effort will come from user fees, not from

Patient-Focused Drug Development Guidance Documents And Target Milestone Dates

GUIDANCE REQUIREMENT UNDER 21ST CENTURY CURES SEC. 3002	PUBLIC WORKSHOP	DRAFT GUIDANCE	FINAL GUIDANCE
Approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy[1,2]	December 2017	June 2018	March 2020
Processes and methodological approaches to develop and identify sets of impacts that are most important to patients[1,2]	December 2018	June 2019	March 2021
Approaches to identifying and developing methods to measure patient impacts that may facilitate collection of meaningful patient input in clinical trials[1,2]	December 2019	June 2020	December 2021
Methodologies, standards and technologies to collect and analyze clinical outcome assessments[1,2]	June 2019	June 2020	December 2021
Procedures for submitting proposed draft guidance relating to patient experience data for FDA consideration	N/A	March 2018	December 2019
Timeframe for FDA response to submissions in the drug development qualification (DDT) program for clinical outcome assessments and patient-reported outcomes (to be encompassed within guidance on implementation of the DDT qualification process)	N/A	December 2019	September 2020
Anticipated use of relevant patient experience data to inform regulatory decision-making, including integration of patient experience data in the benefit-risk assessment framework	June 2019	June 2020	December 2021

[1] Also a commitment in the PDUFA VI agreement.
[2] Format and content requirements for submissions will be addressed within the body of each guidance document.

Source: FDA Plan for Issuance of Patient-Focused Drug Development Guidance Under 21st Century Cures (May 2017)

FDA's Innovation Account established under Cures.

FDA proposes to allocate $2.3m in Innovation Account funding to the patient-focused drug development activities in FY 2018, with the annual allocation topping out at $4.2m in 2025, according to the agency's work plan.

"The agency will strengthen its staff with clinical, statistical, psychometric, and health outcomes research expertise, incorporating these staff into review teams during drug development and application review where sponsors intend to use patient input as part of the development program," FDA said in a footnote explaining how the Innovation Account funds would be used.

"The guidance development work under section 3002 is a top priority for the HHS secretary and for the agency, both to fulfill the statutory mandate and meet the needs of patients," the footnote states. "In view of the close alignment of the content of these statutory requirements and the commitments for guidance proposed under [PDUFA VI], FDA anticipates relying on PDUFA VI fee funding to support the majority of this work."

REGENERATIVE MEDICINE FRAMEWORK COMING SOON

The largest chunk of Innovation Account funding is targeted for implementation of the Cures provisions on patient access to therapies and information, with $23.9m allocated in FY 2018.

These provisions include allowing FDA to rely on qualified data summaries to support approval of supplemental indications, combination product development and innovation, and the establishment of the Regenerative Advanced Therapy Designation (RMAT) program and development of standards for regenerative therapies.

In his blog entry, Gottlieb said FDA has already received almost two dozen requests for RMAT designation, four of which have been granted.

In September, the agency will announce a "comprehensive framework for the development and proper FDA oversight of regenerative medicine," which will be part of the agency's Innovation Initiative, Gottlieb said. "This new policy effort will comprise a series of new guidance documents covering many aspects of the regulation of regenerative medicine products."

Gottlieb's blog also discusses another area of focus in the forthcoming Innovation Initiative – the development and use in silico tools, or computer modeling and simulation, to study and evaluate drugs and devices.

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RB Says Petya Cyberattack Froze Shipments, Could Cost £100M

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Reckitt-Benckiser Group PLC, among organizations in more than 60 countries that were impacted by the June 27 Petya cyberattack, is projecting around £100m in lost revenues for fiscal 2017.

In a July 6 update, the UK-based firm expresses confidence that damage to its applications and systems has been "materially contained." However, "the attack did disrupt the company's ability to manufacture and distribute products to customers in multiple markets across the RB Group," it says.

"Consequently, we were unable to ship and invoice some orders to customers prior to the close of the quarter. Some of the factories are currently still not operating normally, but plans are in place to return to full operation," according to the release.

The global marketer of *Mucinex* expectorants, *Nurofen* analgesics, *Strepsils* throat lozenges and *Enfamil* infant nutrition, as well as *Clearasil* acne treatments and *Veet* depilatories, now expects organic revenue growth of 2% for the full year, down from the 3% previously forecasted.

Based on the firm's fiscal 2016 net sales of £9.89bn ($12.7bn), the cyberattack's cost to RB's business could be in the neighborhood of £100m ($129m).

RB notes that its adjusted guidance also reflects to some degree reduced product orders in India due to a new goods and services tax.

The Petya-variety malware also infected the systems of pharma giant Merck & Co., which tweeted June 27 that its computer network was "compromised as part of a global hack," but provided no further details.

Germany-based **Beiersdorf AG**, which markets the *Nivea* and *Eucerin* skin-care lines, was affected as well. In a July 3 statement, the company said its email and telephone system had been reactivated at most affiliates and no data had leaked as a result of the attack.

"We are well on track to bring our business operations – including production – fully back to normal to provide our consumers and customers worldwide with the service they are used to," it said.

Shutterstock: Ranjith Ravindran

The threat of cyberattacks on biopharma – which has extensive information assets – has moved up to the top of the list of business risks confronting senior management in that field. Biopharma cyber chiefs had a recent roundtable discussion on the risks of cyberattacks to biopharma company competitiveness and the integrity of relationships with key stakeholders, ranging from key customers and suppliers to patients. *(Also see "Hack Attack: Biopharma Cyber Chiefs Fight Back" - Pink Sheet, 25 Jun, 2017.)*

The widely felt attack, which struck government agencies, banks and companies in the Ukraine before sweeping across the globe, used a modified version of malware similar to that seen in May's WannaCry hack, which locked up National Health Service systems in the UK.

While such campaigns typically encrypt data and demand ransom payments in Bitcoin currency, the apparent lack of a financial motive in the June attack, among other details, has many security experts suspecting that a nation state, rather than a criminal organization, is to blame.

Russia has been floated as a possible culprit.

ROUGH FEW MONTHS FOR RB

The cyberattack is ill-timed for RB, whose fiscal 2017 first quarter, reported in April, marked its weakest showing in 15 years.

RB attributed its flat sales performance to a consumer backlash in South Korea and a Scholl rechargeable foot file that flopped.

But the firm seems to have turned a corner in its recovery from the virus, certainly in comparison to where it was in its earliest communications to customers.

On the day of the attack, RB's outlook was considerably bleaker. "The virus is highly potent – it's being investigated by government agencies and the major security and technology firms, and there remains only a limited understanding of it and one firm recommendation on how to cope with it," the firm stated.

The company has since underscored that the attack did not impact systems of its newly acquired Mead JohnsonNutrition Co. business. The $17.9bn deal, which closed less than two weeks before the Petya malware reared its head, added Mead's Enfamil brand to RB's lineup and provided it with a platform to expand sales of its existing health, personal and home care products in China. *(Also see "Reckitt Expands 'OTC' Business, China Presence With Mead Johnson" - Pink Sheet, 13 Feb, 2017.)*

ANALYSTS WEIGH IN

Analysts are of the opinion that even without the cyberattack, RB was unlikely to have achieved its previous target of 3% organic revenue growth for the year.

"The 3% guidance for 2017 organic growth was already looking [like] a stretch (we had +2.3%), but in light of the recent cyberattack we think it prudent to lower

our estimate to +1.6%," says Credit Suisse Analyst Charlie Mills in a July 6 report.

Societe Generale's Jamie Norman, director of the firm's consumer specialist sales unit, offers a similar take on the firm's situation in a same-day analyst report.

"Clearly there will be some questions around whether there are wider problems with RB's model," Norman says. "We continue to see RB as structurally well-placed, as it operates in high-growth, high-gross margin categories and has a gifted and highly incentivized management team. Nevertheless, the market will likely remain skeptical until trading improves."

From the editors of the Tan Sheet.
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LITIGATION

German Isentress Case Could Mean More Compulsory Licensing In Europe

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If upheld, a potentially landmark decision by a German court to allow **Merck & Co. Inc.** a compulsory license to continue selling its HIV/AIDS drug Isentress (raltegravir) could open the door to more cases of compulsory licensing, said Marc Holtorf, head of German intellectual property at the law firm Pinsent Masons.

The case goes back to 2015, when the Japanese firm Shionogi filed a patent infringement action in a Dusseldorf court against Merck, claiming that the US company's marketed integrase inhibitor Isentress infringed Shionogi's German patent DE 60242459.3. The two firms tried to negotiate a license fee to be paid by Merck to Shionogi, but no agreement was reached. For its part, Merck defended itself by attacking the validity of the patent through nullity proceedings. And in a separate move, in 2016, it filed a request for a compulsory license to allow it to continue marketing Isentress.

Germany's Federal Patent Court provisionally granted Merck a license, which meant that the company could keep on marketing the drug. Shionogi appealed this provisional decision, and after fast-track proceedings, the Federal Court of Justice this week upheld the patent court's provisional ruling, which will stand until the case is heard on its merits by the Federal Patent Court.

Holtorf does not expect the patent court to take a different opinion. "My feeling is they have already dug deep in to it and I would be surprised if the [final] outcome is different," he said in an interview with the *Pink Sheet*.

PUBLIC INTEREST?

Compulsory licenses are very rare in Germany, with only one issued to date, which was subsequently revoked. However, this could be set to change and compulsory licensing could become a new element in the legal wrangling over intellectual property rights, thanks to the decision of the Court of Justice on whether a compulsory license is in the public interest.

Holtorf explained that under German law, four requirements must be met in order to win a compulsory license: the license must involve a patent or utility model; the party seeking the compulsory license must show that it will use the patent or utility model commercially; it must be demonstrated that the applicant has tried to obtain a license through negotiations; and the granting of a compulsory license must be shown to be in the public interest.

> "If this is now sufficient to get a compulsory license, it would really be a landmark decision," – Marc Holtorf

In this case, based on expert opinion, the court concluded that granting a compulsory license would be of in public interest. This is because switching to a different medicine could be risky for certain patient groups – including children aged under 12, babies and pregnant women. Holtorf thinks that in this case the requirement was too easily met and that it could be argued that the public interest is in fact relatively small in relation to the general patient population.

"You could say you can always find a certain patient group that needs a drug, a small patient group out of the general population. If this is now sufficient to obtain a compulsory license, it would really be a landmark decision," said Holtorf. "This really needs to be analyzed further, whether this is really what the court wants to say."

The decision only applies to Germany, but if upheld, it could make it easier for Merck to defend its interests in other countries too.

The decision is undoubtedly good news for Merck. "This is potentially now the best outcome because the patent is still valid so no one else can come on the market. It depends on timelines of different proceedings, there is a scenario when, if I were Merck, I would withdraw the nullity action because why would I want the patent to be invalid if I have the compulsory license?" Holtorf added.

Legal wrangling between the two firms is also ongoing in the UK, where Shionogi brought a patent infringement case against Merck regarding the same drug. The court ruled that Shionogi's UK patent was not valid, and the Japanese court is now appealing. *(Also see "Shionogi/Merck HIV Patent Tussle Set To Go Another Round" - Pink Sheet, 30 Nov, 2016.).*

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Medicare Spending Growth Won't Trigger IPAB Cost Reduction Plan

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The fact that IPAB has not been triggered this year is encouraging for biopharma because it poses more of a threat to industry now than it will in the future.

Spending in the Medicare program is expected to stay within targets set by the Affordable Care Act over the next few years, avoiding the need for the Independent Payment Advisory Board or HHS to develop a plan this year for reducing costs in the program starting in 2019.

"Because the projected five-year Medicare per capita growth rate does not exceed the Medicare per capita target growth rate, there is no applicable savings target for implementation year 2019," Centers for Medicare and Medicaid Services Chief Actuary Paul Spitalnic told CMS Administrator Seema Verma in a July 13 letter. The five-year forecast compares average spending growth rates In Medicare to a target based on general and medical inflation rates from 2015 through 2019.

The letter was released in tandem with the 2017 Medicare Trustees report, which includes updated spending forecasts for the program.

The CMS actuaries' conclusion that IPAB action is not triggered this year is significant because some experts, including Spitalnic, had previously predicted it could be. *(Also see "Medicare Cuts Could Come From HHS In 2019 With No IPAB In Sight" - , 23 Jun, 2016.)*

IPAB-required cuts could significantly impact the biopharma industry because of the way the board's activities are defined. IPAB is restricted from proposing cuts to hospitals, rehabilitation and psychiatric facilities and hospices through 2019, which has led analysts to assume that prescription drug spending under Medicare Part D may be one of the prime targets in any plan developed for implementation before then.

IPAB is supposed to work this way: if Medicare per capita spending growth forecasts exceed certain economic growth measures over a five-year period, the board is tasked with recommending a plan to generate savings in the program. If IPAB is not able to do so – as would be the case currently because the board has not been appointed – HHS is required to develop a plan.

The IPAB cost reduction plan would be fast-tracked through Congress and implemented unless Congress develops and passes an alternative within a certain period of time. The many critics of the board have argued it takes too much authority away from Congress, shifting decision-making on Medicare spending policies from the legislative branch to the executive branch.

The 15-member board is to be appointed by the President and must be approved by the Senate. Members to have yet to be nominated, in recognition that Congress would block their approval.

IPAB THREAT LIKELY TO DIMINISH

The fact that IPAB has not been triggered this year is encouraging for biopharma because it poses more of a threat to industry now than it will in the future. In addition to the fact that a broader array of health care providers (beyond biopharma) could face cuts beginning in 2020, the spending target calculation will change beginning in 2018 in a way that is expected to allow for more leeway before the trigger threshold is reached. Instead of an average five-year growth rate, the trigger rate will be calculated at GDP +1%.

Industry "dodged a bullet," Bernstein analysts Tim Anderson commented in a July 13 analyst note. Even though IPAB is unpopular in Congress and the Administration, it could have been used as political leverage in the drug pricing debate, he pointed out.

"The 'trigger' not hitting today is good news for healthcare investors," Anderson wrote. "Despite plenty of bipartisan dislike for IPAB, the industry has been nervous it could have been used as a bargaining chip to levy concessions from the drug manufacturers. While this may still be the case in the future, there is also a good chance that IPAB will be dismantled altogether in the future, eliminating this risk in its entirety."

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Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Pfizer's *Mylotarg* (gemtuzumab ozogamicin) in combination therapy with daunorubicin and cytarabine for the treatment of adults with previously untreated, de novo acute myeloid leukemia	Oncologic Drugs	July 11
Novartis' tisagenlecleucel-T suspension for treatment of pediatric and young adults ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia	Oncologic Drugs	July 12
Amgen's ABP 215, a proposed biosimilar to Genentech/Roche's *Avastin* (bevacizumab)	Oncologic Drugs	July 13 (morning)
Mylan's MYL-1401O, a proposed biosimilar to Genentech's *Herceptin* (trastuzumab)	Oncologic Drugs	July 13 (afternoon)
Intellipharmaceutics Corp.'s oxycodone extended-release tablets, with purported abuse-deterrent properties, for management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time	Anesthetic and Analgesic Drug Products/Drug Safety and Risk Management	July 26
Safety and efficacy of Dynavax's hepatitis B vaccine	Vaccines and Related Biological Products	July 28
Janssen Biotech's *Plivensia* (sirukumab) for adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying anti-rheumatic drugs	Arthritis	August 2
Pfizer's *Xeljanz* (tofacitinib) for treatment of adults with active psoriatic arthritis	Arthritis	August 3

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