Lambda Research Newsletter

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Clinical Research

NEWS letter

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GLOBAL NEWS

1. Clinical trials are compromised by the poor reporting of preclinical research

A study led by researchers at Hannover Medical School, Germany, in collaboration with researchers from McGill University, Canada, suggests that results of human clinical studies are compromised by the poor animal study design and reporting. The authors recommend to the regulatory authorities to develop standards in study design for reporting of animal research evaluating new drugs in trials, as the evidence from animal studies help in ensuring that the patients are not at risk.

The study, published in the journal PLOS Biology, analyzed the descriptions of animal studies found in investigator brochures (IBs), which are the documents used by regulatory authorities and ethics committees to assess the potential efficacy of drugs that are being tested in patients for the first time.

In this analysis, <1/5th IBs referred the preclinical studies, which have been published through peer-review publication process. Furthermore, the measures to minimize the bias in studies such as simple randomization techniques and sample size calculation were reported in <20% of the studies, and negative results were reported in only 4% IBs out of 700 preclinical studies analyzed.

Source: sciencedaily.com

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GLOBAL NEWS

2. Chemical compound inhibiting ebola virus replication identified

A study led by the Georgia State University identified an organic chemical compound that has effective antiviral activity against Ebola and several other viruses. The researchers found that benzoquinoline inhibited the multiplication and reproduction of Ebola virus in cell cultures.

Ebola, a member of the Filovirus family, is an enveloped single strand RNA virus that causes several viral diseases in humans. The Ebola virus outbreak in 2013-2016 in West Africa resulted in >28,000 infection and >11,000 deaths. Currently, there are only experimental treatments available against the virus.

In the current study, researchers screened a library of 200,000 small molecule compounds to identify potential inhibitors of Ebola virus RNA synthesis. A total of 56 hits that inhibited Ebola virus activity by >70% were identified, which also showed <20% chances of being toxic to cells. In total, 3 chemical structures with potent antiviral activity against Ebola virus were identified in cell cultures.

One of these chemical structures, benzoquinoline, showed antiviral activity against Ebola virus and was also active against another deadly filovirus, Marburg virus, vesicular stomatitis virus from the rhabdovirus family and Zika virus.

Source: news.gsu.edu

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GLOBAL NEWS

3. Physician payouts by pharma companies linked to cancer drugs choices

A study conducted in the US suggested that some oncologists may be more likely to prescribe certain cancer medicines when they receive payments from the companies that make these drugs.

A study published in *JAMA internal Medicine* revealed a big association between physician payments with the odds of prescribing that companies' drug. Researchers led by the University of North Carolina scoured the federal database where those financial disclosures are stored, called Open Payments, and discovered a troubling trend: Oncologists treating metastatic kidney cancer or chronic myeloid leukemia (CML) who received payment from a pharma company in 2013, had twice the odds of prescribing that company's drug.

From the available data of 354 physicians who prescribe kidney cancer drugs, 89 took pharma money for consulting, meals, travel and other activities – these payments increased the boost in prescriptions for Bayer's Nexavar and Pfizer's Sutent. Novartis, Pfizer, Bayer and Bristol-Myers Squibb topped the list of companies benefiting from their largesse to the oncology community. The UNC researchers found that the oncologists who treat CML had 29% higher odds of prescribing drugs of the companies who paid them.

Source: fiercepharma.com

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GLOBAL NEWS

4. New antibiotic capable of killing superbugs

Researchers have been successful in synthesizing a “game changing” new antibiotic which is capable of killing superbugs. This new antibiotic could lead to the first new class of antibiotic drugs in 30 years. This synthetic antibiotic is based on teixobactin — a natural antibiotic discovered by US scientists in soil samples in 2015, which has been heralded as gamechanger in the treatment of antibiotic resistant pathogens such as MRSA or VRE.

Scientists from the University of Lincoln, UK, have now successfully created a simplified, synthesized form of teixobactin. They conducted a study to treat a bacterial infection in mice and showed the first proof that such simplified versions of its real form could be used to treat real bacterial infection as the basis of a new drug.

For the development of the synthetic version of the natural drug, researchers developed a library of synthetic versions of teixobactin by replacing key amino acids at specific points in the antibiotic’s structure to make it easier to recreate. These modified structures were shown to be highly potent against bacteria in *in-vitro* or test-tube experiments. Then, one of the synthetic versions was used to successfully treat the superbug in a preclinical study by Singapore Eye Research Institute (SERI).

Source: sciencedaily.com

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PHARMA INDIA

1. Indian Pharma sector may post single digit growth in 2018-2020

According to the rating agency ICRA, Indian pharmaceutical industry is expected to grow at a moderate pace, in single digit, i.e., 7-10% during the year 2017-18 to 2019-20. This slow growth rate is linked to slowed growth in the US because of big drugs going off-patent, and increased competition, among others.

According to the ICRA, revenue growth in the US:

Year	CAGR%
2012-2017	19.3%
2016	14.4% Fall down
2017	16.2% Fall down

The profitability of domestic pharmaceutical companies will be affected by the regulatory scrutiny and consolidation of supply chain in the US market resulting in pricing pressures along with sustained investments in R&D. After mid-to-high double-digit growth in the last five years, the aggregate revenue growth of a sample of 21 companies is reported to be 7-10% in year 2018 to 2020.

FY 2018	Revenue Margin %	Growth rebounded
December quarter	1.5%	7.6%
September quarter	0.8 %	10.3%
June quarter	8.8%	8.8%

Source: Indiatoday.in

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PHARMA INDIA

2. CDSCO plans software database for Pharma manufacturers

The drug regulator is in plans to develop software for improving the rules and regulations for drugs and cosmetics and it is mandatory to all Pharma manufacturers to provide the details of their products including new approved drugs in this software.

The software will be discussed during meeting between center and state drug regulators. Manufactures will have to provide information of their existing facilities and add drugs in to the software, which will be verified by the state regulators. In this software, data regarding the active pharmaceutical ingredients and stocks need to be mentioned. Database is a part of SUGAM which is an e-governance portal; SUGAM still mostly deals with applications for licenses from drug and vaccine makers.

According to the current good manufacturing practices, database is necessary to promote the sharing of information between the centers and all the state regulators. The drug authority should also consolidate the information on clearing and forwarding agents, retailers and pharmacies to better track the medicine's supply chain.

Source: Economictimes.indiatimes.com

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PHARMA INDIA

3. CDSCO plans measurement of drug exports

The Central Drugs Standard Control Organization (CDSCO) has proposed a self-declaration mechanism for pharmaceutical manufacturers for updation of information about the products they manufacture from their registered production centers. This information will be verified by the State Licensing Authority.

According to the proposal, the drug manufacturers licensed to manufacture in India will be asked to upload the details of their manufacturing licenses along with the list of the products permitted under such licenses on an online data base developed by the government, named "SUGAM", which will have all the details of licenses issued, approval and details of manufacturing sites and approved products. The CDSCO has created accounts for each state and is in the process of activation of these accounts to facilitate updating of information.

The proposal of CDSCO is expected facilitate to the ease of doing business in the pharmaceutical manufacturing unit.

The expected grow value mentioned below.

Association	Year	Growth
Pharmaceuticals Export Promotion Council of India	2016-17	$16.8 billion
Pharmaceuticals Export Promotion Council of India	2020	Expected to US$ 20 billion
India Brand Equity Foundation	2025	Expected to $100 billion
India Brand Equity Foundation	2020	Expected to $55 billion

Source: businesstoday.in

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PHARMA INDIA

4. Indian Pharma companies get 51 ANDA approvals from January to March 2018

Indian pharmaceutical companies have been granted 51 (45%) ANDA approvals out of a total 112 approvals from the US Food and Drug Administration (USFDA) between January 2018 and March 2018. Indian companies had grabbed 55 (32%) of 171 ANDAs last year from the USFDA during the same period. Similarly, Indian companies have received 6 tentative ANDA approvals during January-March 2018.

Aurobindo Pharma has been getting the highest number of ANDA approvals amongst the Indian companies with 11 ANDA approvals followed by Strides Shasun 6, Lupin 5, Cipla and Zydus Pharma 4 each; Dr Reddy's Laboratories, Hetero Labs and Taro Pharma 3 each; Macleods Pharma and Vivimed Global 2 approval each; and Alkem Laboratories, Gland Pharma, Glenmark Pharma, Granules India, Jubilant Life, Laurus Labs, Micro Labs and Torrent Pharma one ANDA approval each in the first quarter.

Indian companies are spending large amounts of money on R&D departments to meet the international competition by developing new products.

Source: pharmabiz.com

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REGULATORY ROUND-UP

1. Final guidance from NICE on avelumab from Merck and Pfizer

The National Institute for Health and Care Excellence guidelines support Merck and Pfizer's Bavencio (avelumab) for the treatment of patients with Merkel cell carcinoma (MCC).

The National Health Services provided the approval on funding for use of the drug in patients in whom the disease has spread to other parts of the body and who have previously been treated with chemotherapy.

The MCC is a rare disease with limited treatment options. It was diagnosed in >1,500 people between 1999 and 2008, of which, 79% patients died.

Bavencio (avelumab) is an immunotherapy, works by destroying the cancer cell using patient's own immune system. It was approved as the first and only targeted systemic treatment for metastatic MCC in September 2017.

The Phase II JAVELIN Merkel 200 trial showed durable responses with objective response achieved in 31.8% (28/88) patients; 8 patients showed complete response and 20 partial response.

Source: pharmatimes.com

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REGULATORY ROUND-UP

2. J&J and talc supplier IMERYS to pay fine for mesothelioma case

A jury in New Jersey has ordered Johnson & Johnson and its talc suppliers IMERYS to pay $37 million to a patient, who claimed that asbestos in the product caused his mesothelioma. The company is disappointed with the decision. Johnson & Johnson has already suffered legal losses in cases alleging its talc products triggered ovarian cancer.

The jury is to deliberate and reserve additional comment until the case is completed. The company claims that a regular testing and monitoring has been performed for their products from 1970s, and based on these testing, the company is confident enough that their products are free from asbestoses.

Last year, J&J won a case of mesothelioma in Los Angeles when a shareholder filed a proposed class action lawsuit claiming J&J knew for decades that its talc products contained asbestos fibers and that exposure to them could cause cancers.

Source: Fiercepharma.com

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REGULATORY ROUND-UP

3. New option for medical device companies for 510(k) clearances by FDA

The US Food and Drug Administration (FDA) has published a draft guidance "Expansion of the Abbreviated 510(k) Program: Demonstrating Substantial Equivalence through Performance Criteria". This will set the stage for how an existing 510(k) pathway will be expanded with the goal of providing medical device companies with greater flexibility.

The new option will "modernize the FDA's approach to moderate risk devices by allowing manufacturers to use objective performance criteria to facilitate demonstration of substantial equivalence of their new products to legally marketed devices," – said the FDA Commissioner.

The draft guidance provides details on which devices would be considered appropriate for the new option based on intended use and technological characteristics, how FDA intends to identify performance criteria for the purposes of making final substantial equivalence determinations, as well as what the expectations are for device makers submitting data for FDA review via this program.

Source: raps.org

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REGULATORY ROUND-UP

4. Contraceptive implant Essure slapped with new restrictions by FDA

Essure is the only implanted birth control device for women that does not require a surgical incision. It is just only a flexible coil that is inserted in the vagina, cervix and in the fallopian tubes. After 3 months, tissues are formed around the implants, which create a barrier that keeps sperm away from reaching the eggs.

But these implants may cause severe complications including perforation of the fallopian tubes and uterus, migration of the implants in abdominal and pelvic cavity leading to infection or allergic reactions and depression. Some minor complications are also reported like headache, fatigue, hair loss, weight loss.

The U.S. Food and Drug Administration (FDA) slapped new restrictions on the sale of the permanent contraceptive implant Essure to help curb the associated complications. The step was taken to ensure that all women considering the device "are provided with adequate risk information so that they can make informed decisions," according to an FDA news release.

The agency feels that some women were not fully informed of these risks tied to Essure despite previous significant efforts to educate patients and doctors about the risks associated with this device. Furthermore, the agency said that additional meaningful safeguards are required to ensure women can make informed decisions about the associated risks when considering this option.

Source: consumer.healthday.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

1. Novartis collaborates with gene therapy developer Avexis Inc.

Novartis has entered into an agreement with AveXis, Inc. to acquire the US-based Nasdaq-listed clinical stage gene therapy company. Novartis will pay USD 218 per share or a total of USD 8.7 billion in cash to AveXis, Inc., and the deal is expected to be completed in mid-2018.

This deal is intended to bolster Novartis's neuroscience portfolio and its presence in gene therapy with a promising candidate for type 1 spinal muscular atrophy (SMA) - AVXS-101. AVXS-101 has already generated positive clinical results from a Phase I study and is published in *The New England Journal of Medicine* showing that all SMA type 1 infants who received a single IV dose of AVXS-101 via an adeno-associated virus serotype 9 (AAV9) vector were alive and event-free at 20 months of age. AVXS-101 has been advanced into a pivotal trial in SMA type 1, and in a Phase I trial in SMA type 2.

AVXS-101 has been granted the FDA's Orphan Drug designation for the treatment of SMA, and Breakthrough Therapy designation for SMA Type 1. AVXS-101 has also received the European Medicines Agency's PRIority MEedicines (PRIME) designation for treatments meeting an unmet medical need, as well as Japan's Sakigake designation for breakthrough therapies.

The companies are expected to file a pre-Biologics License Application (BLA) for AVXS-101 with the FDA in the second half of this year, and anticipate the approval and launch in the U.S. in 2019.

Source: novartis.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

2. BE and OSE Immunotherapeutics collaborate on global immune-oncology

Boehringer Ingelheim and OSE Immunotherapeutics have entered into a global agreement to develop OSE-172, a novel checkpoint inhibitor SIRP-alpha antagonist targeting myeloid lineage cells.

OSE-172 inhibits the binding of ligand CD47 receptor SIRP-alpha, and thus, prevents triggering the cellular inhibitory effects of the receptor. According to Boehringer, OSE -172 increases T- cell activity through enhancement of DC antigen presentation functionality, potentiating the phagocytic and inflammatory properties of macrophages in the tumor microenvironment and enabling differentiation of Myeloid-Derived Suppressor Cells to an effector state. With this collaboration, Boehringer Ingelheim strengthens a core pillar of its cancer immunology and immune modulation strategy focusing on novel approaches to treat cancer.

Assuming all milestones are met, OSE stands to receive more than €1.1 billion.

Source: globalpharmaupdate.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

3. Pfizer and Allogene Therapeutics collaborate for CAR T immuno-oncology

Pfizer and Allogene have entered into an asset contribution agreement for Pfizer's portfolio of assets related to allogeneic chimeric antigen receptor T cell (CAR T) therapy. CAR T is an investigational immune cell therapy approach for the treatment of cancer.

Allogeneic CAR T cell therapies have the potential to become the next advancement as one of the most powerful anti-cancer agents, eliminating the need to create personalized therapy from a patient's own cells. These therapies are developed from cells of healthy donors and stored for "off-the-shelf" use in patients, simplifying manufacturing process and reducing waiting time for patients.

Allogene will receive the rights from Pfizer to 16 preclinical CAR T assets licensed from Cellectis and Servier and one clinical asset licensed from Servier, UCART19, an allogeneic CAR T therapy that is being developed for the treatment of CD19-expressing hematological malignancies. In partnership with Servier, UCART19 is initially being developed for acute lymphoblastic leukemia and is currently in Phase I. UCART19 utilizes TALEN® gene editing technology pioneered and owned by Cellectis.

Pfizer will continue to participate financially in the CAR T developments through a 25% ownership stake in Allogene.

Source: pfizer.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

4. Orchard Therapeutics with GSK hands rare disease gene therapies

GlaxoSmithKline (GSK) will hand off its rare disease gene therapy portfolio to two-year-old startup Orchard Therapeutics for a 19.9% stake in the acquirer. GSK will also get undisclosed milestone payments and royalties, and a seat on Orchard's board. The deal also covers GSK's European-approved gene therapy Strimvelis™.

The entire portfolio includes two late-stage clinical programs in ongoing registrational studies—one indicated for metachromatic leukodystrophy (MLD) and the other, Wiskott Aldrich syndrome (WAS) in addition to the exclusive license for three preclinical programs from Ospedale San Raffaele (OSR) and Fondazione Telethon (Telethon).

These programs led to the development of Strimvelis, upon completion of clinical proof-of-concept studies for mucopolysaccharidosis type 1 (MPS1, or Hurler syndrome), chronic granulomatous disease (CGD), and globoid cell leukodystrophy (GLD).

GSK said that it remains committed to developing platform capabilities in cell and gene therapies, but will narrow its focus to oncology, one of the pharma giant's 12 key therapeutic areas of interest.

Source: pharmatimes.com

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DRUGS: APPROVALS AND LAUNCHES

1. Abbvie and Neuroscience's Elagolix gets review extension by USFDA

Abbvie and Neuroscience's uterine painkiller elagolix has got a review extension for marketing application by 3 months from the US Food and Drug Administration (FDA). The regulators have requested additional information regarding the results of liver function tests that were provided by AbbVie when they applied for Elagolix approval in endometriosis-associated pain. The Prescription Drug User Fee Act (PDUFA) date has been extended by three months to Q3 2018.

If the drug is approved by the USFDA, it will be the first new oral medication approved since decades, for the treatment of endometriosis associated pain. Elagolix also has the potential for treatment of endometriosis.

Elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist. It is an oral short-acting molecule that blocks endogenous GnRH signaling by competitive binding with GnRH receptors in the pituitary gland resulting in readily reversible, dose-dependent inhibition of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. This inhibition causes reduced ovarian production of the ovarian sex hormones, estradiol and progesterone.

Elagolix is currently being investigated in uterine fibroids and endometriosis. To date, elagolix has been studied in over 40 clinical trials totaling more than 3,000 subjects.

Source: pharmatimes.com

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DRUGS: APPROVALS AND LAUNCHES

2. Everolimus: Tuberous sclerosis complex associated partial onset seizures

Novartis' medication Afinitor Disperz (everolimus) has been approved by the US Food and Drug Administration for the treatment of tuberous sclerosis complex (TSC) associated partial-onset seizures (POS). Afinitor (known as Votubia® in some countries) is an oral inhibitor of the mTOR pathway. It is the first adjunctive treatment approved in the US for patients aged 2 years and older with TSC-associated POS.

FDA's approval of everolimus was based on the efficacy and safety data from a pivotal Phase III study, EXIST-3 (EXamining everolimus In a Study of TSC). EXIST-3 was a Phase III, three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of low and high exposure ranges of everolimus as adjunctive therapy in patients with treatment-resistant TSC-associated POS. The results of EXIST-3 study showed that when used as an adjunctive therapy, everolimus significantly reduced the frequency of treatment-resistant seizures associated with TSC compared to placebo.

- Median % reduction from baseline in seizure frequency was significantly greater among patients randomized to everolimus low exposure (LE; 29.3%, 95% CI 18.8, 41.9; p=0.003) and high exposure (HE; 39.6%, 95% CI 35.0, 48.7; p<0.001) vs placebo (14.9%, 95% CI 0.1, 21.7).
- Seizure response rate (≥50% reduction) was also greater with everolimus LE (28.2%, 95% confidence interval [CI] 20.3, 37.3) and HE (40.0%, 95% CI 31.5, 49.0; p<0.001) vs placebo (15.1%, 95% CI 9.2, 22.8).
- Most common all-grade adverse events of any cause reported during the core phase at frequencies >15% in the everolimus LE/HE arms included stomatitis, diarrhea, nasopharyngitis, upper respiratory tract infection, and pyrexia.

In the US, the drug is already in the market for the treatment of subependymal giant cell astrocytoma (SEGA) and renal angiomyolipoma

Source: pharmatimes.com

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DRUGS: APPROVALS AND LAUNCHES

3. Tavalisse approved for chronic thrombocytopenia as a first line therapy

Rigel Pharmaceutical Inc. has reported that Tavalisse (fostamatinib disodium hexahydrate) has been approved by the US Food and Drug Administration for the treatment of chronic immune thrombocytopenia – an autoimmune disorder. Tavalisse is a spleen tyrokinase inhibitor; the main target of this drug is to inhibit the autoimmune causes that lead to platelet destruction. Immune thrombocytopenia is very difficult to treat because of its heterogeneity; individual patients have different drug response and resistance.

FDA's approval of fostamatinib was supported by data from the FIT clinical program, which included two randomized placebo-controlled Phase 3 trials (studies 047 and 048) and an open-label extension (study 049), as well as an initial proof-of-concept study.

The new drug application included data from 163 patients with immune thrombocytopenia and was supported by a safety database of more than 4,600 subjects across other indications in which fostamatinib has been evaluated.

Source: ascopost.com

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DRUGS: APPROVALS AND LAUNCHES

4. South Africa's drug approval requires backlog fee to clear pipeline

South African drug makers may be asked to pay a "backlog fee" to help clear a pipeline of medicines waiting years for approval according to a proposal being considered by South Africa's new industry regulator. In South Africa, hundreds of medications are in waiting for approval, which have potent effects against diseases related to cancer, heart diseases and others.

Pharmaceutical companies have been waiting up to 7 years for regulatory decision of their products. The South African Health Products Regulatory Authority's (Sahpra's) proposal to ask a backlog fee may improve access to life-saving medications as well as boost the revenue streams for companies competing in the $3.8 billion-a-year market.

South Africa's pharmaceutical market is forecast to grow at a compound annual rate of 7.3% over the next decade, reaching 87.5 billion rand ($7.3 billion) by 2027 from 45.4 billion rand now, according to BMI Research.

Source: in.reuters.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

1. Novel combination immunotherapy effective for lung cancer

The results of a clinical study published in the journal Lancet Oncology showed that a novel immunotherapy combination is effective and safe at controlling the progression of lung cancer.

The novel drug combination treatment is a combination of checkpoint drug nivolumab with IL-15 agonist ALT-803. Combination of these drugs has been potential, effective, and safe in metastatic non small lung cancer treatment.

“It’s two completely different types of drugs that have never been combined in humans before. The trial demonstrated that these drugs can be safely administered, and also, there’s evidence that it may help patients where checkpoint therapy is not good enough alone,” researchers from the University of South Carolina stated.

Source: sciencedaily.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

2. Pfizer terminates Phase III trial for Inlyta (axitinib)

Pfizer is terminating Phase III clinical trial assessing inlyta (axitinib) in patients at risk of kidney cancer recurrence based on the results from interim analysis that showed no benefit of the drug in this setting.

Inlyta's (axitinib) potential as an adjuvant therapy for patients at a high risk of recurrent renal cell carcinoma (RCC) after nephrectomy was being assessed in the Phase III ATLAS trial. An independent Data Monitoring Committee performed a futility analysis and reported that there was no clear improvement in the primary endpoint of extending disease-free survival for patients treated with axitinib compared to those given a placebo.

Inlyta is an oral kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, which play a role in tumor growth, vascular angiogenesis and progression of cancer. The drug was approved in Europe to treat advanced RCC in patients who have failed to respond to prior therapy with Pfizer's own Sutent (sunitinib) or a cytokine.

Source: pharmatimes.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

3. MSD'S pembrolizumab gets success in clinical trial of NSCLC

MSD's Keytruda (pembrolizumab), when used as monotherapy in the first-line setting, has significantly increased the overall survival in patients with lung cancer expressing any level of PD-L1. These results have significantly increased the treatment scope of the drug.

An interim analysis of the Phase III KEYNOTE-042 that assessed the anti-PD-1 therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) demonstrated a significantly longer overall survival with pembrolizumab than platinum-based chemotherapy in patients with a PD-L1 tumor proportion score (TPS) of ≥1%.

KEYTRUDA® (pembrolizumab) Injection 100 mg

Though Keytruda's initial approval was for use in patients with a TPS of >50%, it remains the only anti-PD-1 approved as monotherapy for NSCLC as a first-line agent.

Source: pharmatimes.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

4. Highland Therapeutics to initiate Phase II testing of nighttime ADHD drug

Highland Therapeutics Inc. today announced the initiation of subject enrollment in a Phase 2 study of HLD100. HLD100 is a new amphetamine-based treatment option for patients with Attention Deficit/Hyperactivity Disorder (ADHD) and is currently under development by Highland Therapeutics Inc.'s wholly owned subsidiary, Ironshore Pharmaceuticals & Development, Inc. ("Ironshore").

Ironshore, that uses that group's proprietary delayed-release and extended-release technology, is conducting this Phase 2 study designed for nighttime dosing of ADHD patients to improve their functioning when they wake.

HIGHLAND THERAPEUTICS

The study will be a "Phase II, Single-center, Open-label, Dose-titration Study Designed to Examine the Safety, Tolerability and Efficacy of Evening Dosed HLD100, a Novel Delayed and Extended Release (DR/ER) Formulation of Dextroamphetamine Sulfate, in Children with Attention Deficit Hyperactivity Disorder" and will enroll 24 pediatric patients, aged 6-12 years.

The HLD100-103 study is part of a comprehensive clinical trial plan being developed for HLD100. Based on data from this study, and on continued feedback and dialogue with the US Food and Drug Administration (FDA), Ironshore anticipates initiating:

1. A Phase 2b/3 study with Vyvanse as a comparator and
2. A pivotal trial program for HLD100.

Source: Fiercepharma.com

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PATENTS: NEW APPROVALS /LITIGATIONS /SETTLEMENTS

1. Sanofi executives face charges for dengue vaccine related suspicious deaths

Complaints about deaths allegedly caused by Dengvaxia, a dengue vaccine by Sanofi, have been filed as families call for criminal charges against officials with the government, Sanofi and distributor Zuellig in Philippines.

There were deaths of four children reported after receiving the controversial dengue vaccine. The Philippine Public Attorney's Office (PAO) helped the families of these children to file their criminal complaints with the Department of Justice against eight Sanofi executives, most of them with local management titles, 15 managers at distributor Zuellig Pharma, and Department of Health (DOH) officials involved in approving and purchasing the vaccine.

The PAO forensic report suggests that the death of four children 11 days to 8 months after vaccination with reports of extensive organ bleeding – a characteristic of Dengue infection,S and have no history of dengue infection.

Sanofi's recent analysis suggested that Dengvaxia could worsen dengue infections in dengue-naïve populations. The Philippine government had to suspend its mass immunization program because of that.

Source: Fiercepharma.com

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PATENTS: NEW APPROVALS /LITIGATIONS /SETTLEMENTS

2. Biogen to launch Humira biosimilar in Europe

Biogen and Samsung Bioepis are in a license agreement with AbbVie to launch a copy of Humira, a critical moneymaker for AbbVie in Europe. The license agreement requires Samsung Bioepis to pay AbbVie royalties on sales of its version. The approved biosimilar of humira—Imraldi—will be launched in the European Union on October 16, 2018.

AbbVie will grant patent licenses for the sale and use of Imraldi in Europe on a country-by-country basis. Imraldi is not yet approved in the United States, but AbbVie stated that it would begin a license period for the biosimilar in the US market on June 30, 2023.

Biogen already markets 2 biosimilars in Europe and the planned introduction of Imraldi on October 16 could potentially expand patient choice by offering physicians more options to meet the needs of patients while delivering significant savings to healthcare systems. Biogen has previously reported that Imraldi's introduction could save European health systems $3.18 billion by 2020.

Source: Fiercepharma.com

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PATENTS: NEW APPROVALS /LITIGATIONS /SETTLEMENTS

3. Patent litigation settlement for LINZESS (linaclotide)

Ironwood pharma and Allergen has reached an agreement with Aurobindo pharma to resolve a patent litigation related to Linzess. Aurobindo pharma has filed an abbreviated new drug application (ANDA) for the approval to market the generic version of Lizness (linaclotide) before expiration of the applicable patents. This is the second patent related to Lizness for which the companies have reached a settlement.

Ironwood and Allergan will permit Aurobindo Pharma, a license for marketing the generic version of Lizness in the US in beginning of August, 2030 under this settlement. It is subjected to the U.S. FDA approval until completion of law procedures, according to the terms and settlement of the law.

Linaclotide is a guanylate cyclase-C (GC-C) agonist that binds to the GC-C receptor locally, within the intestinal epithelium and is indicated for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC).

Source: pharmpro.com

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PATENTS: NEW APPROVALS /LITIGATIONS /SETTLEMENTS

4. Amendment sought for Sec 146 of Patents Act, 1970

Several leading pharmaceutical organizations from India as well as abroad have sought amendment to Section 146 of the Patents Act, 1970, to ensure that patent working disclosures under that section complement other provisions of India's patent laws. This will foster the ongoing efforts to increase the ease of doing business in India. Furthermore, it will increase patent office efficiency, and do not burden Indian patent owners.

The logic behind strengthening the Section 146 of Patent Act, 1970 is that it is outdated, unclear and it creates more predictableness. The major clarity should in the Section 146 when the invention has been in India according to the joint statement by the Organization of Pharmaceutical Producers of India (OPPI), Pharmaceutical Research and Manufacturers of America (PhRMA), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), and Japan Pharmaceutical Manufacturers Association (JPMA).

According to Section 146, patent office is required to publish a Form 27, which has not been updated from the last 45 years, thus, do not reflect today's globalized nature of innovation and patenting activity, and the pharmaceutical associations are concerned that third parties can abuse Form 27 disclosures to misappropriate legitimate intellectual property rights.

Source: pharmabiz.com

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TECHNOLOGY /NDDS

1. FDA permits artificial intelligence-based device to detect diabetic retinopathy

The U.S. Food and Drug Administration (USFDA) permitted the first artificial intelligence based medical device to measure greater than a mild level of the eye disease diabetic retinopathy in adults with diabetes.

The IDx-DR (device) is a software program that uses an artificial intelligence algorithm to analyze the mages of the eye taken with a retinal camera called the Topcon NW400. A doctor uploads the digital images of the patient's retinas to a cloud server on which IDx-DR software is installed.

If the images are of sufficient quality, the software provides the doctor with one of two results:

- more than mild diabetic retinopathy detected: refer to an eye care professional or
- negative for more than mild diabetic retinopathy; rescreen in 12 months

If a positive result is detected, patients should see an eye care provider for further diagnostic evaluation and possible treatment as soon as possible.

The FDA approved the device based on the results of a study where data of 900 patients having diabetes were analyzed. In the study, IDx-DR was able to correctly identify the presence of more than mild diabetic retinopathy 87.4% of the time and was able to correctly identify those patients who did not have more than mild diabetic retinopathy 89.5% of the time.

Source: fda.gov

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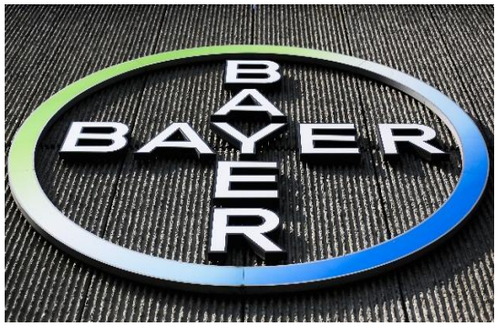
TECHNOLOGY /NDDS

2. DelSiTech and Bayer partner to develop innovative drug delivery

Bayer is contracting with Finland's DelSiTech for the development of new drug delivery technology for the treatment of eyes.

Under this licensing deal, Bayer will shell out milestone payments and royalties to DelSiTech as drugs using its technology make their way through development and onto the market. Bayer will also cover expenses through the process.



DelSiTech's system is based on a biodegradable silica matrix. An active ingredient is embedded on the matrix and the dissolution of the matrix does not change the pH in the surrounding tissue, which is a major risk with the other drug delivery systems.

The collaboration with DelSiTech is part of Bayer's recent push to team up with other companies developing cutting-edge science in ophthalmology. Some of the examples are Eylea, a blockbuster macular degeneration treatment co-developed with Regeneron, and Johns Hopkins University for new therapies for retinal diseases.

Source: Fiercepharma.com

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TECHNOLOGY /NDDS

3. New drug delivery by bacteria carrying red blood cells

Researchers at the Max Planck Institute for Intelligent Systems in Germany develop a new device which combines the bacteria with red blood cells (RBCs) which will be able to ferry cargos in a rapid way to the desired spots in the body.

The RBCs are used to hold the cargo within their cytoplasm, while the bacteria provide the motor power to travel throughout the body. The natural properties of RBCs, microswimmers in this case, are maintained hence, they are able to squeeze through capillaries much narrower than themselves.

They are also loaded with iron nano-particles in order to guide the hybrid devices to their destination due to the resultant magnetic forces. This has been tested in the laboratory and they are further going to test these in animal models and in humans in the very near future.

Source: fiercepharma.com

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TECHNOLOGY /NDDS

4. FDA approves world's smallest mechanical heart valve for pediatric patients

The US Food and Drug Administration (FDA) has approved Abbott's Masters HP™ 15 mm rotatable mechanical heart valve (world's smallest mechanical heart valve) for the treatment of toddlers and babies when needed with mitral or aortic valve replacement.

Until now, only a range of larger-sized valves were used to replace a pediatric heart valve that could not be repaired. This new small sized valve is the first and only pediatric mechanical heart valve developed for newborns and infants in whom the only treatment option is to replace the valve.

The Masters HP™ 15 mm rotatable mechanical heart valve is a rotatable, bileaflet mechanical heart valve designed for implantation in the mitral or aortic position and is part of the Masters Series line, which now includes seven valves with diameter sizes ranging from 15 to 27 mm. The valves have pyrolytic carbon leaflets and orifice rings, an 85-degree leaflet opening angle to improve flow and reduce turbulence, and a controlled torque rotation mechanism for rotation and intraoperative adjustment. A sewing cuff contains additional suture markers for more accurate placement.

Source: prnewswire.com

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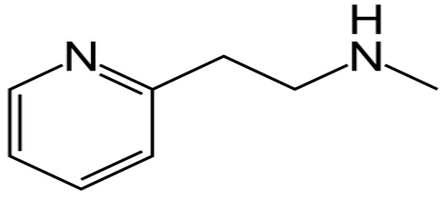
WHAT'S NEW AT LAMBDA

1. Method for the quantization of betahistine in human plasma

INTRODUCTION

Betahistine is a vasodilator, and is most commonly used to treat the symptoms of Meniere's disease, vertigo and tinnitus.

Betahistine chemically is 2-[2-(methylamino) ethyl] pyridine and is formulated as the dihydrochloride salt.



Mono amino oxidase metabolizes betahistine rapidly to its major metabolite 2-pyridylacetic acid (2-PAA). Hence, 2 PAA concentration is widely used as a surrogate pharmacokinetic (PK) measurement for betahistine concentration.

We, at Lambda, have developed and validated a novel and highly reproducible bioanalytical method to quantify the concentrations of parent betahistine and its metabolite.

Due to its metabolism into 2-PAA, betahistine is unstable in blood but it can be stabilized with MAOI (monoamine oxidase inhibitor) at highly controlled low temperatures. We have used one of the MAOI to stabilize betahistine in the plasma. Betahistine has a low molecular weight and considering its highly polar nature, chromatographic separation is also challenging.

To achieve low picogram detection and chromatography separation, we used an ion pairing reagent. The current analytical method describes the LC-MS/MS analysis of betahistine in human plasma containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) as anticoagulant.

Adequate method sensitivity and selectivity were achieved by monitoring distinct precursor to product ion mass transitions for Betahistine. This method is highly sensitive and also selective for its major metabolite 2-PAA

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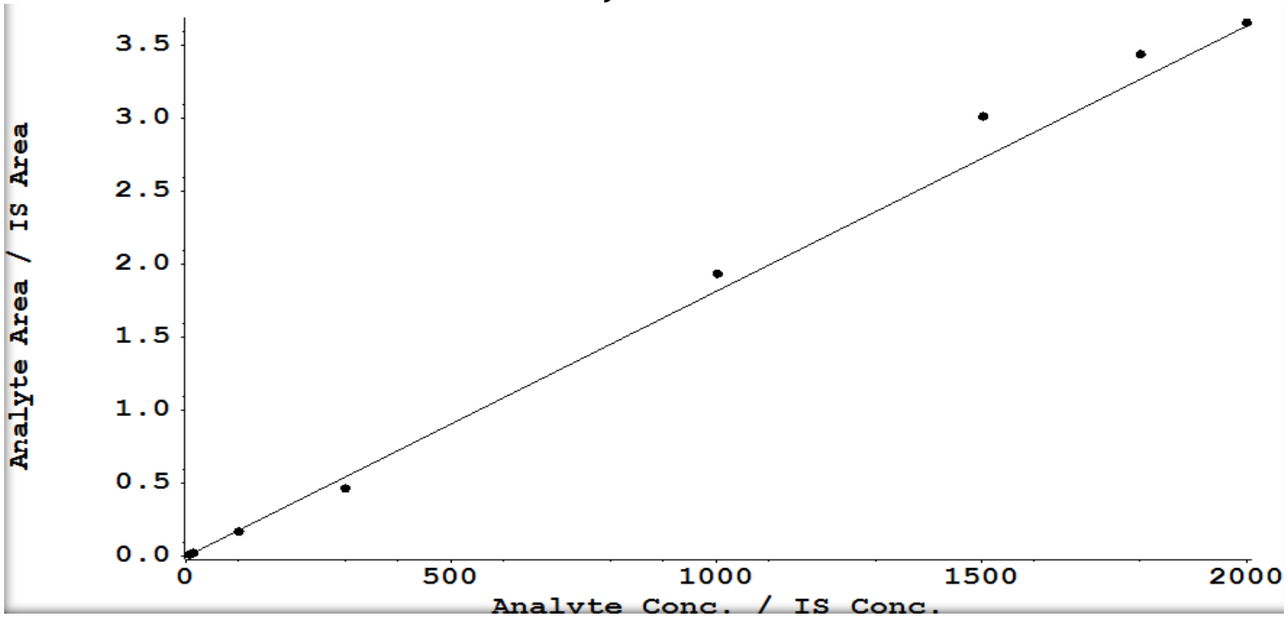
WHAT'S NEW AT LAMBDA

METHOD IN BRIEF	PRECISION & ACCURACY			
SPE • low volume plasma • 7.5 pg/mL LLOQ • Run Time: 7.0 mins • No Carry Over • Selective from its major 2-PAA metabolite.	LOQ QC	LQC	MQC	HQC
	7.9951	21.8152	567.8529	1509.9566
	±0.71420	±1.00483	±18.79935	±66.54201
	8.9% CV	4.6% CV	3.3%CV	4.4% CV
	106.2% THR	98.6% THR	92.5% THR	95.1% THR
	n=18	n=18	n=18	n=18

- **Method Available for Immediate Bio-Analysis**



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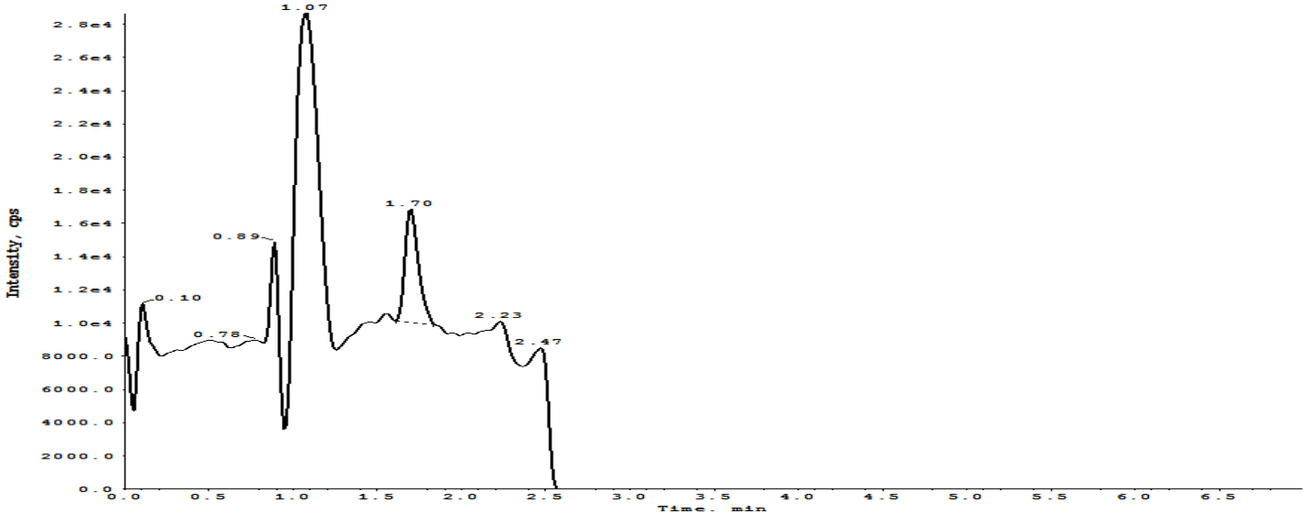
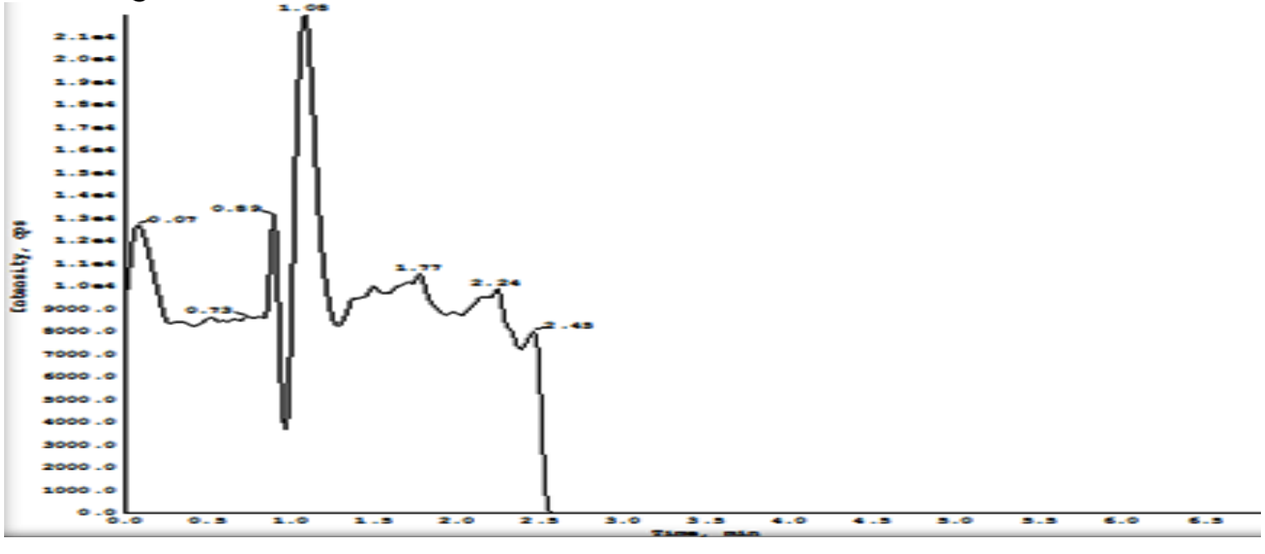
WHAT'S NEW AT LAMBDA

Chromatogram of LLOQ



Chromatogram of Blank Plasma



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WHAT'S NEW AT LAMBDA

2. Biz-Net version 6.0 launched

Lambda manages its clinical trial data through Biz-Net, which is a clinical data management system (CDMS). Recently, Biz-Net has been updated with 6.0 version, which has been successfully implemented across Lambda. Some of the major modifications are listed below:

- Case Report Form (CRF) designing as per Study Data Tabulation Model (SDTM) parameters
- Data export in SDTM format
- Cumulative audit trail of Patient Information File (PIF) is also provided in addition to field wise audit trail

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WHAT'S NEW AT LAMBDA

3. Audits @ Lambda

USFDA Audit
The USFDA made an inspection on 23rd April 2018 for the clinical phase of bioanalytical/bioequivalence (BA/BE) studies, where 4 studies were randomly selected. There was no finding or discussion points rose pertaining to the clinical conduct as well as the process/study data by the USFDA inspectors. The USFDA issued a form 483 for one bug in software regarding gunning of label for which an appropriate documentation was already made during study in the study data. The identified bug has been updated in system.

The USFDA had another inspection for a patient based BIO study where Lambda was responsible as a CRO. The USFDA inspector walked in without prior intimation at two sites. 483 observations were issued; those were already responded by clinical investigator. They are minor in nature.

NPRA Audit
The National Pharmaceutical Regulatory Agency (NPRA) Malaysia completed the inspection for Clinical & Bioanalytical department at Lambda Ahmedabad in the month of August 2017, which was successful and is now closed. Lambda is now a qualified CRO for Malaysian regulatory submissions.

WHO Audit
The World Health Organization (WHO) completed the inspection of Lambda Ahmedabad BA/BE facility (in-house BA/BE studies) in March 2018. The WHO inspectors have closed the audit with no open items.

CAP and NABL Accreditation
Lambda clinical pathology lab has completed NABL (National Accreditation Board for Testing and Calibration Laboratories) inspection successfully. In the month of December 2017, the College of American Pathologists (CAP) audited the Central Clinical Lab and was completed successfully. Lambda laboratory has been accredited by both CAP and NABL.

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