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MAY 2020

PHARMACOALERT
NEWSLETTER

Drug Safety Alert, New Drug Marketed, Drug Interactions And Banned Drugs

Contents

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LUCKNOW

From The Desk of Editorial Team

The department of Pharmacology, Dr. RMLIMS, Lucknow, is pleased to present the May issue of our newsletter. As we all are aware that the world is yet to tide over the pandemic therefore in our current issue also, we are continuing with the new relevant updates on the use of drugs in COVID-19 along with our regular features on Pharmacovigilance, New drug approvals.

The first section remains dedicated to the Updates pertaining to Corona. In this current situation of the COVID 19 pandemic, there is no specific treatment who are sick with coronavirus and no vaccine to prevent the disease, but we have tried to round up some of the research on COVID 19 that has emerged recently and produced results that may hopefully help tackle the global pandemic. In our last feature, we discussed the recent progress of vaccine and we have continued our efforts to provide more updates on vaccines which researchers hope to fight the new coronavirus. This issue also presents detailed information on Remdesivir, an Ebola drug and its potential to treat COVID19. In our drug update column, we have discussed about drugs which have recently been in headlines for their role in treatment protocol of COVID-19. Also, to note we have featured an article on Quality Management System and Artificial Intelligence (AI) in Pharmacovigilance (Pv) and its future strategies. Quality management and AI are new approaches for enhancing the future of Pv for better data quality and consistency which ultimately improves the outcome of Pv data for patient safety.

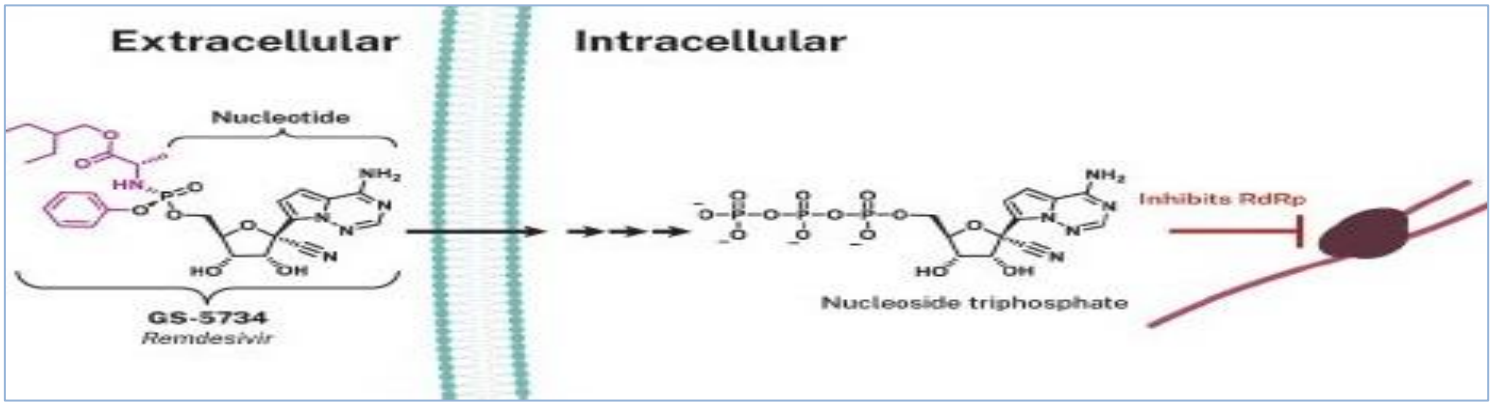
Though each of these, information has been taken from authentic sources but due to the everchanging scenario and new information pouring in everyday, the information given may appear to be insignificant. Hope that you shall understand the situation and bear with us for any such inadvertent matter.

We would like to conclude with Sir William Osler's quote "One of the 1st duties of physician is to EDUCATE THE MASSES", as it proves very important in this present pandemic with soaring high cases which necessitates us to educate our surrounding people for preventive measures and strictly follow as still we are living in ray of hope of definitive treatment.
Keep reading and Stay Safe

REMDESIVIR IN COVID-19

The global pandemic of COVID-19, caused by SARS-CoV-2, has driven the biomedical community to uncover and develop newer interventions. One such therapeutic approach which has been currently granted regulatory approval is Remdesivir which is an experimental antiviral drug developed by Gilead for use against Ebola. However, a large phase 3 study conducted in the republic of Congo showed Remdesivir to be less effective in preventive deaths from the Ebola viruses which lead to its uncertain future. But with the outbreak of SARS-CoV2 and no definitive treatment in sight, series of experiments in human cell cultures and mice were conducted that indicated Remdesivir could have activity against coronavirus like MERS and probably COVID-19. Also, clinical trials have shown Remdesivir may improve recovery time for people with moderate to critical COVID-19.

Mechanism of Action: Remdesivir (GS-5734), a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate, a nucleoside triphosphate derivative (NTP). It interferes with the action of viral RNA-dependent RNA polymerase and evades proof reading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production.



Recommend Dose: As per the clinical management protocol of COVID-19, Govt. of India, Remdesivir can be administered via an intravenous injection (IV) with a loading dose on day 1 (200 mg in adults, adjusted for body weight in paediatric patients) followed by a daily maintenance dose (100 mg in adults) for up to 5 days.

Use in Special populations:

Pregnancy: Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Renal Impairment: Use in patients with renal impairment are based on potential risk and potential benefit considerations. Patients with GFR greater than or equal to 30 mL/min have received Remdesivir for treatment of COVID-19 with no dose adjustment of Remdesivir.

Hepatic Impairment: Hepatic laboratory testing should be performed in all patients prior to starting Remdesivir and daily while receiving Remdesivir.

Contraindications

- Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of Remdesivir.
- AST/ALT > 5 times Upper limit of normal (ULN)
- Severe renal impairment (i.e., eGFR< 30ml/min/m2 or need for haemodialysis)
- Pregnancy or lactating females
- Children (< 12 years of age)

Adverse Drug Reactions: Limited safety data is available for Remdesivir. Most common are fever, anaemia, acute kidney injury, decreased eGFR or creatinine renal clearance or increased blood creatinine, hyperglycaemia and increased transaminase.

REGISTERED REMDESIVIR TRIALS FOR SARS-COV-2/COVID-19

S.N.	Title	Status	Study Results	Conditions	Interventions
1.	Adaptive COVID-19 Treatment Trial (ACTT)	Recruiting	No Results Available	SARS-CoV-2/COVID-19	Remdesivir; Remdesivir placebo
2.	Public Health Emergency SOLIDARITY Trial of treatments for COVID- 19 Infection in Hospitalized Patients	Available	Results Available	SARS-CoV-2/COVID-19	Remdesivir; Lopinavir/ ritonavir; Lopinavir/ Ritonavir, Interferon β-1a; Hydroxychloroquine; standard of care
3.	Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections	Recruiting	No Results Available	COVID-19	Drug: Remdesivir
4.	Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age with Coronavirus Disease 2019(COVID-19)	Not yet recruiting	No Results Available	COVID-19	Drug: Remdesivir
5.	Study of Merimepodib in Combination with Remdesivir in Adult Patients with Advanced COVID-19	Recruiting	No Results Available	COVID-19	Drug: Merimepodib Drug: Matching Placebo Drug: Remdesivir
6.	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in participants With Severe Coronavirus Disease (COVID-19)	Active, not recruiting	No Results Available	COVID-19	Drug: Remdesivir Drug: Standard of Care

REGISTERED REMDESIVIR TRIALS FOR SARS-COV-2/COVID-19

S.N.	Title	Status	Study Results	Conditions	Interventions
7.	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	Active, not recruiting	No Results Available	COVID-19	Drug: Remdesivir Drug: Standard of Care
8.	A Trial of Remdesivir in Adults With Mild and Moderate COVID-19	Suspended No Results	Available	COVID-19 SARS-CoV-2	Drug: Remdesivir Drug: Remdesivir placebo
9.	A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia	Recruiting No Results	Available	COVID-19 Pneumonia	Drug: Remdesivir Drug: Tocilizumab Drug: Placebo
10.	A Trial of Remdesivir in Adults With Severe COVID-19	Terminated No Results	Available	COVID-19 Remdesivir SARS-CoV-2	Drug: Remdesivir Drug: Remdesivir placebo
11.	Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (COVID-19)	Available	No Results available	SARS-CoV2 Infection	Drug: Remdesivir

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2. *Yeming Wang, MD, Dingyu Zhang, MD,Prof Guanhua Du, PhD, Prof Ronghui Du, MD, Prof Jianping Zhao, MD,Prof Yang Jin, M Det al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Volume 395 Issue 10236 P1564-1578, MAY 16,2020*
3. *For latest information on clinical trials that are testing the use of remdesivir in COVID-19, please visit www.clinicaltrials.gov.*

COVID-19 News Board -Drug Update

Medicines That Made Headlines Lately

Parameters	Favipiravir	Remdesivir	Dexamethasone
Type of medicine	Antivirals		Steroid
Mechanism in COVID-19?	Works by inhibiting an enzyme called RNA dependent RNA polymerase. This enzyme plays an important role in replication of coronavirus. Restricting it means less viral copies leading to reduced number of viruses, less damage in the body, and thus hypothesized to achieve quicker recovery.		Recent evidence suggests that a subset of patients with severe COVID-19 may have cytokine storm syndrome which is a condition frequently related to lung involvement (including ARDS) and multi-organ failure. In order to induce immunosuppression to antagonize virus driven hyperinflammation, in these patients, a therapeutic role has been hypothesized for corticosteroids Animal experiments are being conducted to support and also provide evidence for the use of glucocorticoids during the acute phase of severe disease to (i) reduce inflammation, (ii) attenuate acute lung injury, and (iii) improve survival.
Current status worldwide	Approved in Japan for novel influenza strains unresponsive to available antivirals Unlicensed in US and UK; Emergency Use Authorization given	Granted (only) Emergency Use Authorization (EUA) by Food and Drug Administration (FDA) to treat adults and children hospitalized with severe COVID-19	Approved in UK to treat all people hospitalized with COVID-19, who require oxygen, including those on ventilators Unlicensed in US for the indication, exclusive recommendations for use of dexamethasone in people with COVID-19 have been released by the National Institutes of Health.

COVID-19 News Board -Drug Update

Medicines That Made Headlines Lately

Parameters	Favipiravir	Remdesivir	Dexamethasone
Current status in India	Drug Controller General of India (DCGI) has given approval to a pharmaceutical company (Glenmark, Brand name: Fabiflu) for manufacturing and initiation of Phase III Trials in India	Emergency Use Authorization provided to two pharmaceutical companies, Hetero Health Care (Brand name, Covifor)and Cipla (Brand name, Cipremi)	The Ministry of Health and Family Welfare has included Corticosteroids in the updated clinical management protocol for COVID-19, after considering the latest available evidence and expert consultations. Guidelines on Clinical Management of COVID – 19 by Ministry of Health and Family Welfare. For patients with progressive deterioration of oxygenation indicators, rapid worsening on imaging and excessive activation of the body's inflammatory response, glucocorticoids can be used for a short period of time (3 to 5 days). It is recommended that dose should not exceed the equivalent of methylprednisolone 1 – 2mg/kg/day. Note that a larger dose of glucocorticoid will delay the removal of coronavirus due to immunosuppressive effects. ICMR has taken a cautious approach towards the use of dexamethasone and is conducting its own trials since as per the experts, in India, the number of patients on ventilators is lower than the number of patients who require oxygen while on dexamethasone. Safety profile of corticosteroids in people with COVID-19 and having any pre-existing conditions remains unclear.

COVID-19 News Board -Drug Update

Medicines That Made Headlines Lately

Parameters	Favipiravir	Remdesivir	Dexamethasone
Who would benefit	People having mild-to moderate Coronavirus disease	Emergency use for the treatment of people hospitalized with COVID-19.	People who are hospitalised with severe respiratory complications of COVID-19, put on ventilator or oxygen support
ADRs/Contraindications (Caution advised)	Hypersensitivity to Favipiravir Pregnancy and breastfeeding mothers Elderly and children, unless advised by your doctor	Hypersensitivity to Remdesivir Severe impairment in kidney functions High level of liver enzymes Pregnant and Lactating women Children below 12 years of age	Immunosuppression with long term exposure Systemic fungal infections Hypersensitivity to dexamethasone Cerebral malaria Caution in certain conditions like cirrhosis, myasthenia gravis, renal insufficiency, or ulcerative diseases such as peptic ulcer disease or ulcerative colitis. and people at higher risk for osteoporosis Cautious use during pregnancy and lactation

Umifenovir Drug Trial

CDRI Lucknow has got approval from the Drug Controller General of India to begin trials on the anti influenza drug Umifenovir. The premier drug institute shall begin its drug trial on the drug Umifenovir on the COVID positive persons/patients.

The trial began in the last week of June with initial 130 patients.

CDRI has tied up with Dr Ram Manohar Lohia Institute of Medical Sciences, King George Medical University and ELMCH for initiating the trials.

The trial has been designed to be Randomized double blind placebo-controlled trial for testing the efficacy, safety and tolerability of the drug

Quality Management System and Artificial Intelligence in Pharmacovigilance

Quality of drugs safety data plays an important role as Pharmacovigilance (Pv) is one of the components for ensuring patient safety. The drug safety data collected through various stakeholders of Pharmacovigilance Programme of India (PvPI) requires mandatory analysis and decision making. Therefore, **Quality Management System (QMS)** and quality data management documentation plays a vital role in Pv.

The need for the quality and accuracy of the data collected in Pv system has been considered important to maintain the drug safety. As if the safety of a product is to be assessed and monitored properly, then clearly the company, regularly authorities and consumers must have confidence in the quality and accuracy of the data used to make that assessment. An established quality system is adequate and effective for performing Pv activities which should cover organizational structure, responsibilities, procedures, processes including appropriate resource management, compliance management and record management based on **quality planning, quality control, quality assurance and quality improvements in a documented, systematic and orderly manner**.

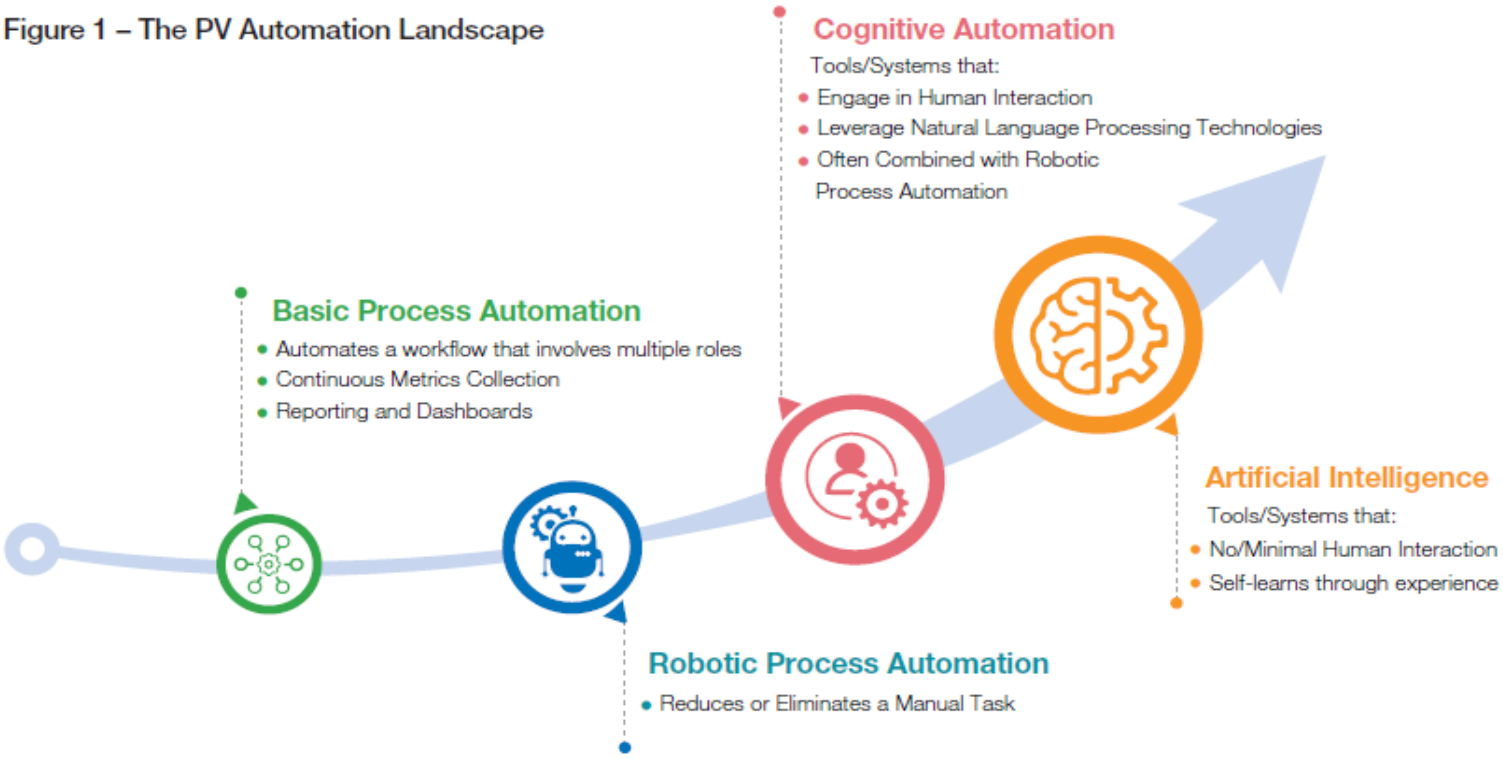
The challenges of establishing and maintaining progressively more complex Pharmacovigilance (Pv) systems in a globally diverse and evolving regulatory environment are increasing day by day. As more and more drugs receive regulatory approval there is growing public awareness, social media connectivity and scrutiny. Pv activities need to be managed more diligently and efficiently than ever.

Effective Pv entails critical coordination of numerous end-to-end safety surveillance activities from individual case management through aggregate reporting, signal detection, benefit-risk evaluation and risk minimization. Typically, thousands of adverse event (AE) cases are processed manually by global case processing teams, involved in data entry, quality review and medical review of individual case safety reports in the safety database. Some of these are reported on an expedited basis to regulatory authorities by submission teams. In addition, periodic aggregate reporting to regulators worldwide involves the review of cumulative safety information from a wide range of sources. Specialized domain experts further focus on complex safety areas like signalling, benefit-risk evaluation and risk minimization activities for safety issues.

Technological overlay in the form of off-the-shelf, customized or home grown solutions for case intake, processing and submission, as well as tools for data mining and analytics, enabled quality organization and successful delivery of Pv programs and enrich innovation to support changing global needs.

The first step towards Pv transformation is the process of mapping and evaluation to drive process improvements, making end-to-end safety processes leaner as well as better and eliminating non-value adding and redundant steps in existing processes. It is essential to integrate global systems and processes, which lend themselves to further automation for efficiency gains and quality improvements. To achieve full Pv transformation, multiple stages or levels of automation are required to ensure processes are completed correctly. **Starting with basic automation, through robotic process automation, to cognitive computing and eventually leading up to Artificial Intelligence (AI).**

Figure 1 – The PV Automation Landscape



Artificial Intelligence (AI) is a subfield of computer science in which a computer system is taught to perform tasks that normally require human intelligence. Natural language processing (NLP) is the ability of a computer system to understand and interpret human language. Machine learning is an area of AI that gives computer systems the ability to learn without explicitly being programmed. Cognitive services are the combination of both NLP and machine learning algorithms that aim to solve specific tasks that would otherwise require human intelligence. In order to develop cognitive services, an annotated corpus or data used to teach the cognitive service must be prepared and created. The Pv value chain can be augmented by AI with the aim of decreasing cognitive burden and supporting efficiencies in various Pv processes

The methodology for implementing cognitive services consists of (1) conducting contextual analysis (2) assessing human cognitive workload (3) determining decision points for applying AI (4) defining the scope of the data or annotated corpus required for training and validation of the cognitive services (5) identifying and standardizing Pv knowledge elements (6) developing cognitive services and (7) reviewing and validating cognitive services.

The value of using AI methodologies in Pv is compelling; however, as Pv is highly regulated, acceptability will require assurances of quality, consistency and standardization. There is a need to identify assistive technologies that provide the automation of repetitive tasks involved with the collection and collation of AEs as well as providing support and evidence to enhance complex decision making within Pv. New technology options should be able to automate mundane activities, harness and provide a synthesized view of the growing amount of data and provide evidence of recommendations to a Pv professional. AI can reduce the manual effort associated with transcription and data entry to allow greater focus on scientific and medical evaluation of AEs, work that ultimately brings greater value to the patient.

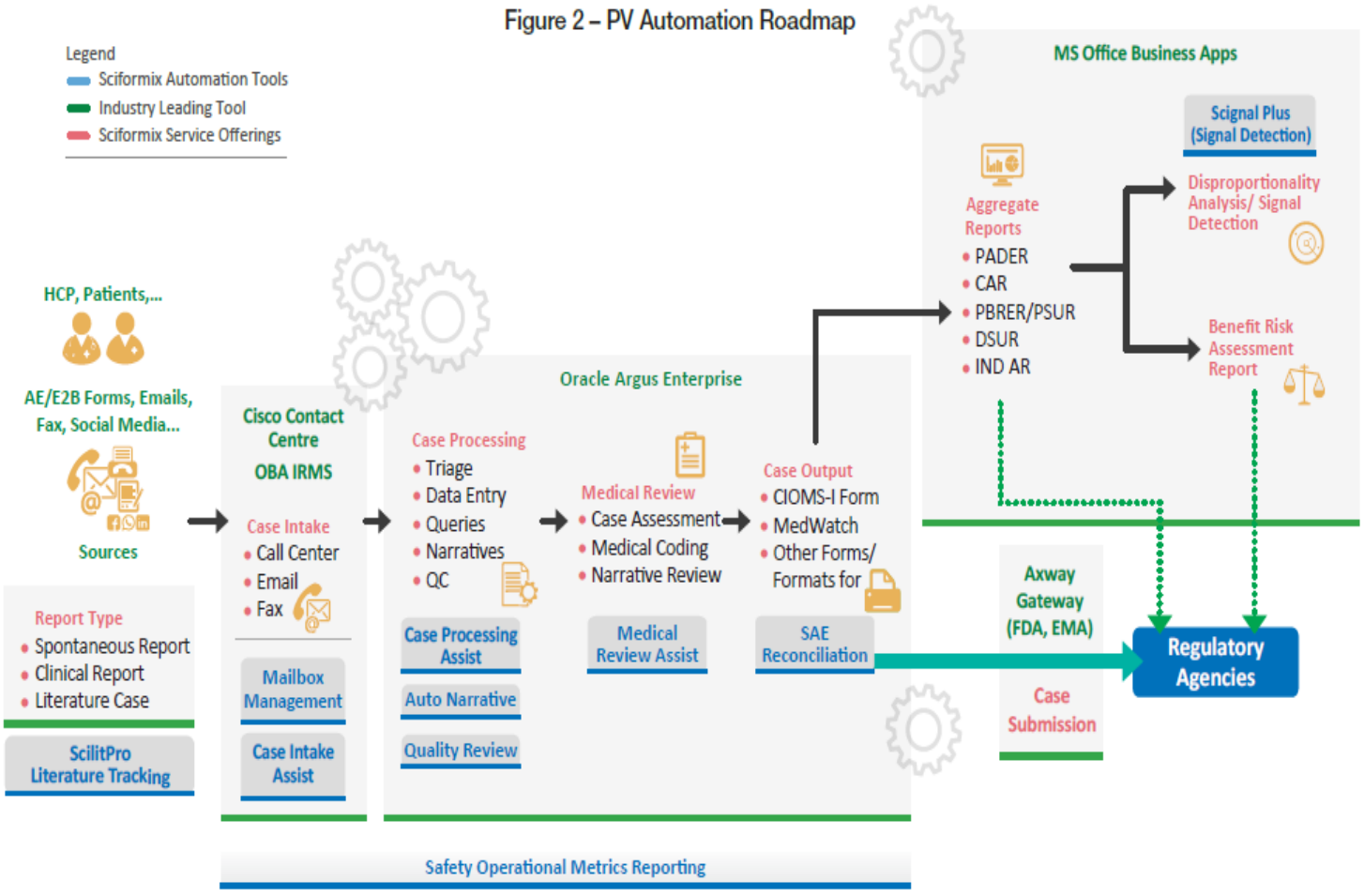
As automation becomes more prevalent within Pv, the focus will decrease on repetitive tasks and data collection creating more opportunities to concentrate on evolving regulatory requirements and complex healthcare cases. Patient safety is central to Pv, and in the space in which AE reports are becoming more frequent and more convoluted, it is imperative that innovation and technology are intertwined to create quality data that will promote patient benefit and health. The Pv industry has needed a long-term solution to unsustainable volumes of Individual Case Safety Reports (ICSRs), and by embracing AI it is possible to improve the way we approach Pv and strive for excellence in our processes for the benefit of the patient.

There are three key areas within the safety realm, which can be transformed through the appropriate and effective use of technology-

- Standardization and automation of Pv processes and safety data management is required to gain efficiencies while maintaining quality and compliance.
- Proactive Pv and risk minimization to identify and predict emerging safety signals is possible by implementation of data mining techniques to bolster safety analytics, reporting and investigation.
- Fostering open and transparent data sharing with regulators, prescribers and patients is required to build public trust and confidence. The **US FDA Sentinel system, EMA's Eudra Vigilance database and WEB-RADR** are examples of how to implement tools that allow for full data transparency.

Strong technical and Pv knowledge is key to successfully navigate the highly regulated space while delivering comprehensive end-to-end automation solutions, specifically geared for the management of Pv activities. For optimal Pv management, a clear and robust vision must be established with strategies and initiatives with specified milestones to track progress to reach the defined end goals. Pv delivery, safety technology and regulatory reporting including call center, case data entry, literature review, aggregate reporting and Pv quality assurance will go a long way in enabling this vision of transformation.

Figure 2 – PV Automation Roadmap



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New Drug Approvals (May 2020)

SNo	Drug	Mechanism of Action	Indication	Date of Approval
1	Capmatinib	Inhibitor of the proto-oncogene c-Met (also known as hepatocyte growth factor receptor (HGFR)) c-Met, is a receptor tyrosine kinase overexpressed or mutated in many tumor cell types which have been found to pla key roles in tumor cell proliferation, survival, invasion, metastasis, and tumor angiogenesisSelectively binds to c-Met, thereby inhibiting c-Met phosphorylation and disrupting c-Met signal transduction pathways. Induces cell death in tumor cells overexpressing c-Met protein or expressing constitutively activated c-Met protein.	To treat patients with non small cell lung cancer	6/5/2020
2	Selpercatinib	Selpercatinib is a direct Rearranged during transfection (RET) kinase inhibitor, exhibiting IC50 values between 0.92 and 67.8 nM depending on the exact RET genotype. Information based on natural as well as induced resistance mutations and molecular modelling suggests that selpercatinib directly inhibits RET autophosphorylation by competing with ATP for binding. Selpercatinib is also reported to inhibit other tyrosine kinase receptors, including VEGFR1, VEGFR3, FGFR1, FGFR2, and FGFR3, at clinically relevant concentrations	To treat lung and thyroid cancers	8/5/2020
3	Ripretinib	Ripretinib binds to KIT and PDGFRA receptors with mutations on the exons 9, 11, 13, 14, 17 and 18 (for KIT mutations), and exons 12, 14 and 18 (for PDGFRA mutations).The “switch pocket” of a protein kinase is normally bound to the activation loop, acting as an “on-off switch” of a kinase. Ripretinib boasts a unique dual mechanism of action of binding to the kinase switch pocket as well as the activation loop, thereby turning off the kinase and its ability to cause dysregulated cell growth	To treat advanced gastrointestinal-stromal tumors	15/5/2020
4	Fluoroestradiol F18	Estrogen receptor (ER)-positive breast cancers are a subset of breast cancers in which the cancerous tissue expresses estrogen receptors - these receptors provide a useful target for imaging and treatment agents. Fluoroestradiol F-18 is a fluorinated analog of estradiol that binds to estrogen receptors, allowing for PET imaging of lesions	Diagnostic imaging agent for certain patients with breast cancer	20/5/2020
5	Artesunate	Artesunate is metabolized to the active DHA, the endoperoxide bridge of DHA reacts with heme, generating free radicals which inhibit protein and nucleic acid synthesis of the Plasmodium parasites during all erythrocytic stages. Reactions with these free radicals can also lead to alkylation of parasitic proteins such as a calcium adenosine triphosphatase and EXP1, a glutathione S-transferase.	To treat severe malaria	26/5/2020
6	Flortaucipir F18	Flortaucipir F-18 is a small molecule that contains radioactive 18F, which decays by positron emission to 18O with a half-life of 109.8 minutes.6 As a small relatively lipophilic molecule, flortaucipir F-18, following intravenous injection, quickly passes through systemic circulation, crosses the blood-brain barrier, and binds to neurofibrillary tangles (NFTs) . Once bound, the ensuing radioactive decay emits pairs of 511 keV gamma photons useful in diagnostic imaging. The pattern and intensity of emission during imaging is used in the diagnosis of Alzheimer's disease.	Diagnostic agent for patients with Alzheimer’s disease	28/5/2020