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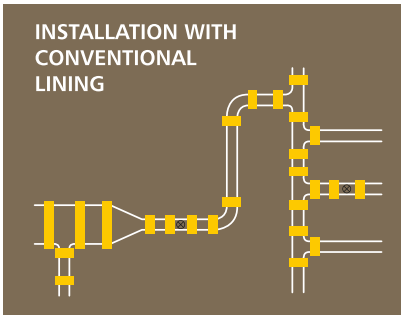

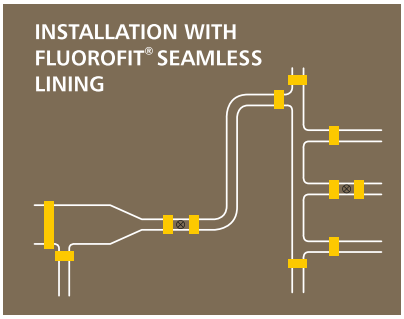

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BDR Pharma launches Nintenib (Nintedanib) to treat Idiopathic Pulmonary Fibrosis in India

BDR Pharmaceutical announced the launch of 100mg and 150 mg Nindetanib under the brand name Nintenib for the treatment of Idiopathic Pulmonary Fibrosis (IPF). Nintenib is priced at INR 750 (100 mg) and INR 900 (150 mg) for a pack of 10 tabs.

Idiopathic pulmonary fibrosis (IPF) is a lung disorder where there is scarring of the lungs from an unknown cause. It is usually a progressive disease with a poor long-term prognosis (1). The median survival in IPF patients is 2.5 to 3.5 years. Nintedanib received DCGI approval after showing a significant slowdown in the disease progression in patients with pulmonary fibrosis by reducing the rate of decline in forced vital capacity (FVC) in patients with IPF and mild or moderate lung function impairment.

Currently, there are two clinical trials being conducted to study the safety and efficacy of Nintedanib for the treatment of moderately to critically ill COVID-19 patients suffering from IPF.

Mr. Dharmesh Shah, CMD, BDR Pharmaceuticals said, "We are thrilled to innovate and work towards introducing newer, effective and affordable treatment options for patients. We are proud to launch the generic version of the drug for lung fibrosis in India especially during a time when there is an ardent need of the medicine for COVID-19 patients. With the launch of Nintedanib, we are on the verge of changing the therapeutic dynamics in the segment of tyrosine kinase inhibitors".

Nintedanib is a small molecule tyrosine kinase inhibitor, targeting vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) involved in signaling pathways which lead to its use in pulmonary fibrosis. It has also shown significant efficacy in the management of non-small cell carcinoma of the lung as well as systemic sclerosis.

PCR Biosystems introduces kit for reliable quantification of libraries prepared for Illumina® NGS systems

PCR Biosystems, the UK-based PCR experts, have expanded their range of specialist molecular biology kits with the introduction of NGSBIO Library Quant Kit for Illumina®. The new kit contains all the components necessary for accurate and sensitive quantification of DNA libraries prior to next generation sequencing (NGS) with Illumina platforms. Employed for the vast majority of NGS, the Illumina system requires quantification of libraries prior to sequencing to ensure the correct amount of library is loaded into the machine. This is essential for generating the maximum amount of clustering

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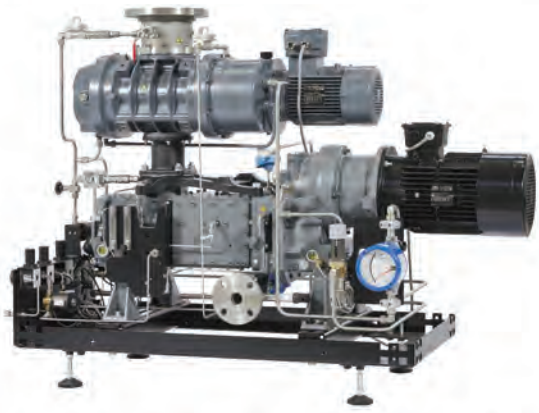

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data possible per run, saving valuable time and money. An easy-to-see blue version of the kit has also been launched, containing a blue qPCR mix for greater pipetting precision and accuracy.

Mark Stevens, Head of R&D explains, " qPCR is the most accurate technique available for library quantification, ensuring optimal cluster densities for improved sequencing efficiency and data quality."

NGSBIO Library Quant Kit offers consistent and reliable quantification across a wide range of sample types, concentrations, fragment sizes and GC content. The kit contains 5 DNA standards, primers specific to the P5 and P7 Illumina adapter sequences, a convenient library dilution buffer and qPCRBIO SyGreen Mix or qPCRBIO SyGreen Blue Mix. The blue qPCR mix contains a non-reactive dye to improve reaction mix visibility and is particularly useful when using small reaction volumes or white plates.

PCR Biosystems also provide a free online calculation tool to help scientists quickly and easily analyse results generated with the NGSBIO Library Quant Kit. While anyone can benefit from this tool, it is particularly valuable to those who are new to NGS. Users can download the results in a pdf, or email the results to themselves with the additional benefit of accessing the data online for up to 30 days.

Sanofi Pasteur Launches Tetraxim®, the First Full-Dose DTaP Booster Vaccine in India for Preschoolers

Sanofi Pasteur India, the vaccines global business unit of Sanofi announced the launch of Tetraxim® (DTaP-IPV). The booster vaccine is indicated for preschoolers and provides protection against four major diseases - Diphtheria, Pertussis, Tetanus and Polio. Tetraxim® combines four vaccines into one, thus reducing the number of injections, increasing comfort and improving vaccination compliance for children and reducing parental anxiety.

As immunity against Diphtheria, Tetanus, and Pertussis wanes over time, it is important to ensure necessary protection by being up to date with booster vaccinations. A vaccine containing full-dose antigens stimulates adequate immune response with better tolerability. This ensures preschoolers receive the right vaccine with the appropriate antigen content at the right time and have sustained protection against disease.

With Tetraxim®, Sanofi Pasteur currently protects school children in more than 100 countries, with 63 million doses distributed worldwide. Annapurna Das, COUNTRY HEAD, INDIA, Sanofi Pasteur said, "Booster vaccines are designed to boost the immunity acquired during prior vaccination. It works as a reminder for a child's immune system and can also stop the spread of infection to their siblings and grandparents, making it important to maintain vaccination schedules of preschoolers."

Delaying or missing vaccinations means children are unprotected for longer than they need to be, often at the time when they are most at risk of illness and serious complications from diseases. The timing of vaccine doses is carefully chosen based on years of research to help protect children at the right time. To ensure complete protection, children should follow the vaccination schedule and ensure that the appropriate dose vaccine is administered.

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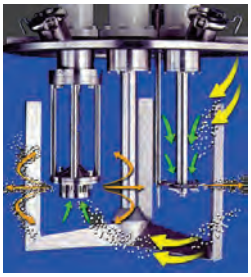

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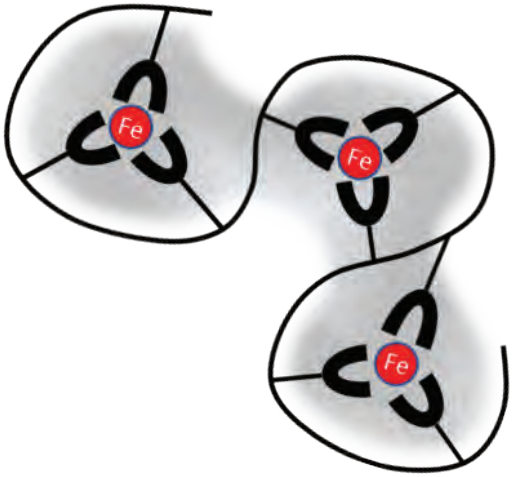
Chelation Partners' Preclinical Anti-infective Polymer Improves Survival in Bacterial Sepsis



Each molecule of the iron binding polymer, DIBI, completely binds three iron molecules, preventing their use by microbes for growth and the generation of damaging reactive oxygen species.

Chelation Partners, a preclinical company focused on medical indications related to iron availability including infectious disease, cancer and inflammatory disorders, today announced the publication of positive preclinical results in an experimental animal model of fatal bacterial sepsis. The study investigated DIBI, a non-toxic, iron chelating polymer with the ability to inhibit growth of a wide variety of microorganisms, including those resistant to antibiotics, by starving them from the freely available iron they need to grow, which DIBI withdraws from the host. DIBI also has anti-inflammatory effects.

Publication highlights for Chelation's Anti-infective polymer:

- DIBI reduced leukocyte adhesion, improved capillary blood flow, and decreased key plasma cytokines levels, important markers of efficacy in sepsis.
- In this model, DIBI improved survival of infected mice, and greatly improved survival when used in combination with the antibiotic, imipenem.
- 7-day survivors treated with only 2 doses of DIBI and imipenem were completely free of systemic infection.

Previous studies of DIBI in other sepsis models have shown it preserved capillary perfusion, reduced plasma inflammatory markers and attenuated tissue damage. In response to the current pandemic, DIBI is also being developed as a potential daily IV therapy for hospitalized COVID-19 patients, to be administered early to suppress the progression of dysregulated inflammatory response (cytokine storm and ARDS (acute respiratory distress syndrome) and secondary infections, pathologies seen in nearly all fatal COVID-19 cases.

DIBI is part of a platform of iron binding polymers Chelation Partners is developing for a wide variety of infectious disease applications as well as anti-inflammatory and oncology indications. The highly soluble nature of these polymers makes a wide variety of formulations and delivery methods possible; DIBI has been delivered to the ear, nose, lung, skin, peritoneally, orally and intravenously in animal models. Veterinary indications are also under investigation and a real-world clinical study in dogs recently showed that DIBI alone was equivalent to the current standard of care, a combination of two antibiotics, in treating otitis externa.

MeaningCloud Announces Completion of Spin-off of its Healthcare and Pharmaceutical AI business to Konplik Health

MeaningCloud announced the completion of a spin-off from its Artificial Intelligence (AI) businesses into a new, independent company. The spin-off will allow both product and management teams to drive increased

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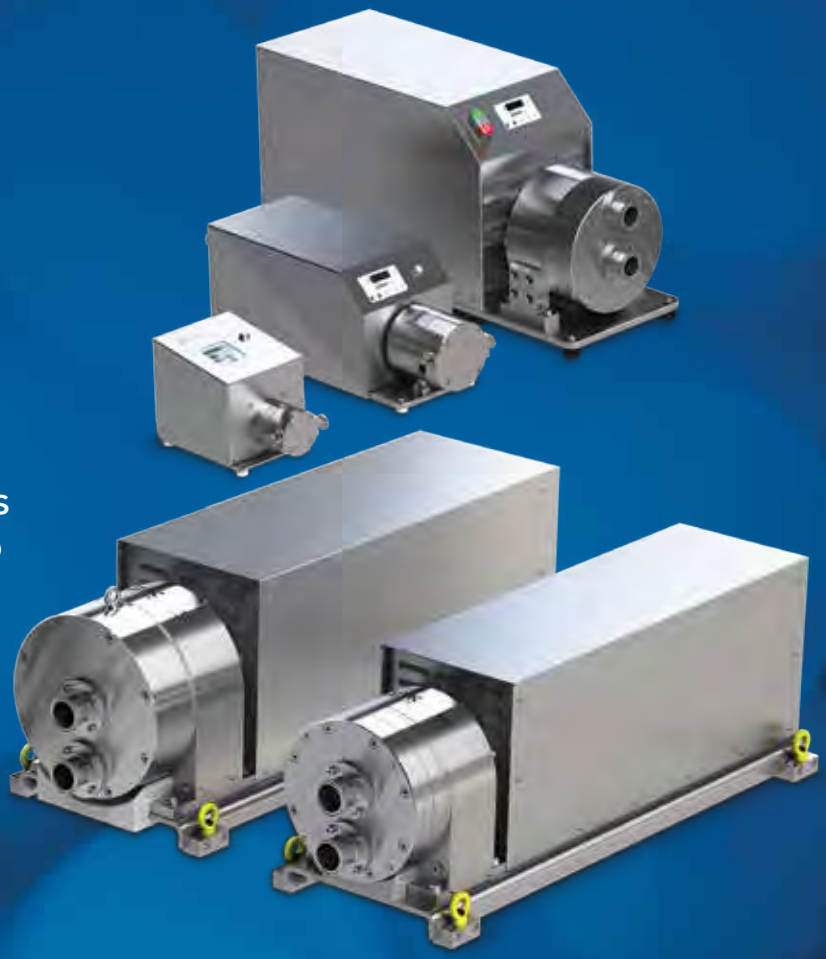

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responsiveness to customers' particular needs and achieve faster growth through focused and fit-for-purpose operating models. Konplik Health, Inc. will begin operations immediately with the health-related assets from MeaningCloud, including its leading text analytics, deep semantic analysis, and AI platform, adaptations specific to the life sciences and relevant clients such as Pfizer. Konplik will be dedicated exclusively to the health care, life sciences, and pharmaceutical sectors.

"We're happy to provide the market with a health-focused AI solution," says Jose Gonzalez, CEO of Konplik Health. "Together with our customers, we're leveraging powerful, adaptive intelligence to create solutions that seamlessly integrate data and technology to automate tasks and enable better decisions."

Konplik specializes in Robotic Process Automation and Predictive Analytics that rely on the ability to understand large volumes of textual data. There are many examples from Konplik's 20-years of history in Natural Language Processing and analytics.

Exemptions of respiratory patients to use face masks are not evidence-based

There have been many false health news, hoaxes and biased information about the ongoing COVID-19 pandemic circulating on the net, and also in printed media and on TV. However, sometimes confusion and misinformation occur through official channels. And it can have serious consequences.

One of them is the exemption for respiratory patients to use a facemask, mandatory elsewhere for everyone both in shared outdoor and indoor spaces since May 2020. The Spanish and British laws state:

"Those persons who present some type of respiratory difficulty that may be aggravated by the use of the mask, and those whose use is contraindicated for health or disability reasons, are excepted from this obligation."

At the Respiratory Effectiveness Group (REG), an independent global group of medical doctors and researchers in Spain, the United Kingdom and many of the EU member states, the United States, Canada and Australia, among others, have reviewed the available evidence. In an article published today in the European Respiratory Journal (accessible from https://doi.org/10.1183/13993003.03325-2020), one of the most prestigious international journals in the respiratory arena, it was concluded that there is no evidence to support this exception, and that patients with a respiratory disease are at a high risk of suffering severe COVID-19, in Spain, the UK and elsewhere. We must succeed in eliminating this exception.

Not using a mask to avoid an asthma attack, or exacerbations of COPD, or of other respiratory diseases, due to an alleged increase in inspiratory pressures through a mask, is unfounded. It is estimated there are 545 million people worldwide suffering a chronic respiratory disease, and not wearing a face mask may carry increased risk of personal and group infection.

Two out of three leading COVID-19 vaccine initiatives utilising Generis's Life Science Platform, CARA

Generis, the global leader in content information management systems, is proud to announce that two out of the three leading COVID-19 vaccine initiatives in Operation Warp Speed are using the CARA Life Science

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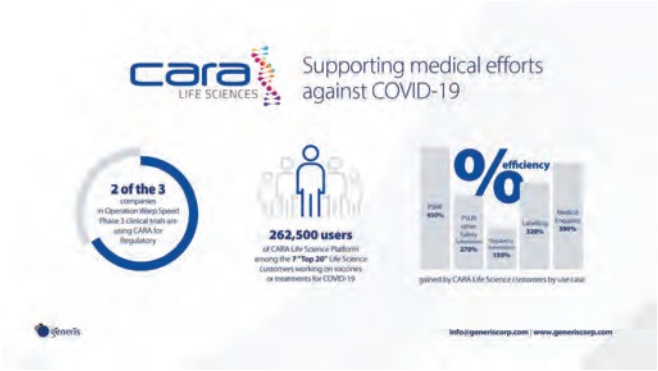


Platform for Regulatory. The US-driven international initiative to support the rapid development, manufacturing, and distribution of COVID-19 vaccines is progressing with many promising efforts to move towards Phase 3 clinical trials. The CARA Life Sciences Platform, provided by Generis, is helping these Life Science companies to greatly reduce their development and submission cycles while focusing on oversight and compliance with stringent health regulations.

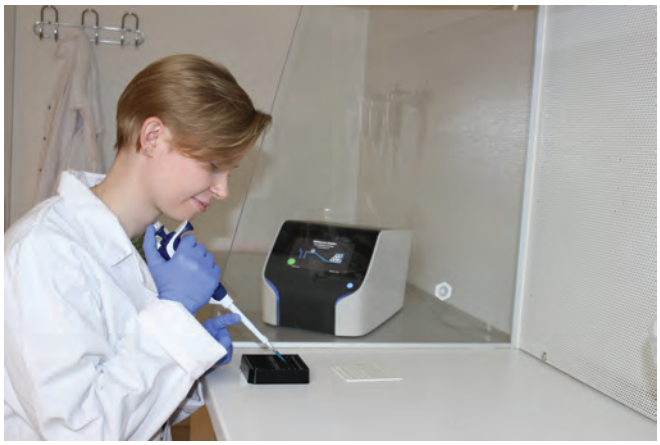
The CARA Life Sciences Platform manages regulated business processes, managing content and data across the core functional areas of Life Science companies. Adoption of this platform has driven process efficiency improvements of up to 450%*, greatly reducing time-to-market for regulated products.

Suriname developed a high quality plasma COVID-19 treatment procedure

The Academic Medical Center (AZP) in Paramaribo, Suriname, successfully studied an efficient method to collect COVID-19 antibody-containing plasma from recovered Covid-19 patients to treat critically ill patients. In contrast with prevailing plasma donation strategies, the Academic Medical Center collects plasma from recovered patients before hospital release. Early in the recovery process, the antibody titer is up to ten times higher than later in recovery. Preliminary data shows excellent results, both in patients where the condition is worsening to critical as for patients recently submitted to ventilator support.

The plasma donation and plasma preparation is supported by the innovative Dutch blood filter HemoClear. In a sterile, simple, and cost-effective procedure, this filter separates plasma from red blood cells. The plasma is processed to treatment for multiple COVID-19 patients while the red blood cells are or could be re-infused to the donor, not to hinder further recovery.

Samplix CRISPR Validation Services – In-Depth Validation of CRISPR-engineered Samples by the Xdrop™ Experts



Caption: Samplix now offers CRISPR Validation Services using the Xdrop™ platform.

Samplix launched a new service to inject transparency into today's cutting-edge gene editing technology, CRISPR. The service team receives, handles and manages samples of engineered genomes. Using Xdrop™ Indirect Sequence Capture, they enrich long DNA fragments that contain a carefully designed Detection Sequence placed 5–10 kb from the CRISPR edited site. They then sequence the enriched DNA as long reads on the Oxford Nanopore sequencer and as short reads on

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an Illumina platform to reconstruct in detail any structural rearrangements, SNPs or other unintended modifications.

Xdrop™ is Samplix' proprietary technology to enrich genomic regions longer than 100 kb from as little as 1 ng genomic DNA and with single-molecule resolution. Unlike other target enrichment methods, Xdrop™ requires knowledge of only a short sequence within or flanking the target region for efficient target selection. Following targeted selection, multiple displacement amplification is applied to single DNA molecules compartmentalized in droplets. This ensures unbiased amplification of large DNA fragments that are representative of the target variation in the original sample.

Plasmacluster Technology Demonstration Effectiveness in Reducing Airborne Novel Coronavirus (SARS-CoV-2), a World's First

For the first time in the world, a device, developed by Sharp Corporation, equipped with Plasmacluster technology, which exposed an airborne novel coronavirus (SARS-CoV-2) to Plasmacluster ions for approximately 30 seconds, has effectively reduced the infectious titer of the virus by more than 90%. This achievement was accomplished in collaboration with Professor Jiro Yasuda of the National Research Center for the Control and Prevention of Infectious Diseases/Institute of Tropical Medicine, Nagasaki University, Professor Asuka Nanbo (a board member of the Japanese Society for Virology) of the same institution, Professor Hironori Yoshiyama of the Department of Microbiology, Shimane University, Faculty of Medicine (also, a board member of the Japanese Society for Virology), and Nagasaki University, an internationally respected authority on infectious diseases research.

In 2004, Sharp demonstrated the effectiveness of Plasmacluster technology against feline (cat) coronavirus, a member of the Corona viridae family. In the following year of 2005, Sharp also demonstrated its effectiveness against the original SARS coronavirus (SARS-CoV), which caused the outbreak of 2002-2003 and is also genetically similar to the novel coronavirus (SARS-CoV-2). Now, Sharp has demonstrated its effectiveness against SARS-CoV-2 in airborne droplets.

Lonza Launches the PyroCell Monocyte Activation Test System for Reliable and Sustainable in vitro Pyrogen Testing

Lonza Bioscience has announced the commercial release of the PyroCell™ MAT System, a sustainable and reliable solution for in vitro pyrogen testing. The new offering expands upon Lonza's experience in primary cells and endotoxin testing, combined with Sanquin's expertise in MAT production, helping ensure the safety of parenteral pharmaceuticals during development, manufacture and product release.

The PyroCell™ MAT System provides advantages over existing methods for pyrogen detection in complex formulations, such as human vaccines and cell-based biologics. It provides sensitive pyrogen detection without the use of experimental animals, thereby supporting sustainability objectives while helping to deliver safe products to the market.

Through a collaboration with Sanquin Reagents B.V., Lonza's PyroCell™ MAT System is comprised of pooled, cryopreserved Peripheral Blood Mononuclear Cells (PBMCs) specifically developed for use with the MAT. These cryopreserved PyroCell™ Kit PBMCs eliminate the need to qualify blood donors and

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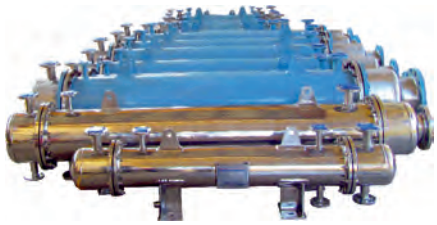

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undertake cell isolation for each single test run. With the PyroCell™ MAT System, the cells can be available on demand whenever the need arises.

The PyroCell™ MAT System reagents can now be purchased throughout North America and Europe through Lonza's comprehensive distribution network and sales support services.

Gerresheimer includes Stevanato Group integrated twist-off closure system solution for Gx RTF syringes

Gerresheimer will offer its Gx RTF syringes with SG ITC (Integrated Tip Cap) twist-off closure of the Stevanato Group. With this technology, which is often asked for on the market, Gerresheimer includes an especially user-friendly system solution for Luer Lock syringes in its program.

The integrated seal cap consists of two components: an elastomeric component, which is available in different formulations and a rigid, translucent polymer cap. The elastomer component is inserted into the plastic cap, screwed together with a Luer Lock adapter, and pre-assembled on the syringe. Compared to traditional Luer Cone systems, this solution offers a syringe closure with increased stability, thus protecting the drug product. The twist-off closure system responds to the containment needs of different drugs: vaccines, hyaluronic acid, biotech drugs and other viscous drugs. It has been developed and produced according to ISO 11040-7 standard and fit perfect on Gx RTF syringes. Gerresheimer will offer 1.0 ml long and 1.0 ml short Luer Lock syringes with the integrated twist-off closure in the first step. Additional formats will follow.

Increased safety and user-friendliness for medical specialists

The seal cap is securely screwed onto the Gerresheimer Luer Lock syringe, so that accidental removal of the cap is prevented. The familiar twist-off function offers medical specialists improved user-friendliness without impairing the integrity of the pre-fillable syringes. The structured surface simplifies the removal of the cap. "We combine our syringes with system components that are primarily aimed at user-friendliness and safety," Manfred Baumann (Global Executive Vice President Sales & Marketing, Administration & TCC, Member of the Management Board, Gerresheimer Regensburg GmbH) explains. "The new SG ITC twist-off closure suits these aims outstandingly." Gerresheimer already delivers syringes equipped with the seal cap, which can be processed on existing filling lines, under the name Gx TWILC (Twistable Integrated Luer lock Closure). The 100-hole nests are packaged in a tub and sterilized with ethylene oxide gas (EtO).

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Piramal Pharma Announces Completion of 20% Strategic Growth Investment by Carlyle

Piramal Pharma Limited (PPL), a subsidiary of Piramal Enterprises Limited received INR 3523.40 Crores on closure of the transaction for 20% equity investment from CA Alchemy Investments (formerly known as CA Clover Intermediate II Investments), an affiliated entity of CAP V Mauritius Limited, an investment fund managed and advised by affiliated entities of The Carlyle Group Inc. ("Carlyle"). The transaction values the Pharma Business at an enterprise value (EV) of US$2,775 million with an upside component of up to US$360 million depending on the company's FY21 performance. This transaction is one of the largest private equity deals in the Indian pharmaceutical sector. It provides PPL growth capital that enables it to invest in accelerated business growth through both organic and inorganic opportunities.

PPL's business now effectively includes:

(a) Piramal Pharma Solutions, an end-to-end contract development and manufacturing (CDMO) business

(b) Piramal Critical Care, a complex hospital generics business selling specialized products across over 100 countries

(c) Consumer Products Division, a consumer healthcare business selling over-the-counter products in India

(d) PEL's investment in the joint venture with Allergan India, a leader in ophthalmology in the domestic market and Convergence Chemicals Private Limited.

This fresh growth investment into Piramal's pharma business will be used as growth capital for the pharma businesses to expand capacity across PPL's sites as well as to tap attractive acquisition opportunities within and outside India.

Cytel ushers in new era of optimized clinical trial design with launch of Solara™

Cytel Inc. has launched Solara™, a collaborative decision-support platform that revolutionizes the identification of optimal clinical trial designs for greater business results for biotech and pharmaceutical companies. The patent-pending platform applies massive cloud computing power to Cytel's proven statistical design engines to explore an exponentially larger study design space than is possible using traditional methods. The new platform also integrates critical non-statistical considerations and uses interactive visuals to streamline collaboration. Until now, such comprehensive exploration was not possible given compressed clinical development timeframes and currently available trial design software. The platform marks a fundamental shift in the way that development teams approach clinical trial design, enabling the planning of faster, more cost-effective trials. Early usage of Solara has consistently uncovered opportunities to reduce trial duration by 10-20% without compromising cost or probability of success.

Developing and bringing a therapeutic to market has become increasingly competitive, putting clinical development teams under significant pressure to create efficient trials that effectively address patient needs. Frequently, such teams lack sufficient time and resources to fully explore, compare and select the most promising design options to meet both clinical and business goals. They may also lack the communication tools that would allow them to succinctly convey to other stakeholders the benefits and trade-offs

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inhouse

of design options in the context of business priorities and constraints. Reaching a consensus can thus be a daunting and lengthy process. Solara is the first tool to enable investigation of the entire relevant study design space to support increased clinical development productivity.

Indica Labs announces launch of enterprise-wide, cloud-based digital pathology deployment at NCI

Indica Labs, a leading provider of computational pathology software and services, are pleased to announce the formal launch of an enterprise-wide, cloud-based deployment of Indica Labs' software within the National Cancer Institute (NCI), including HALO®, HALO AI, HALO Link and HALO AP. Accessible to hundreds of users within the NCI, managing millions of digital images, and facilitating the analysis of thousands of images daily, this is the largest single deployment of Indica Labs' software world-wide.

While NCI has invested in multiple HALO licenses dating back to 2014, the existing on-premise licenses were siloed and generally only accessible to specific research groups. The cloud deployment was designed to merge and harmonize these disparate deployments, to expand the analysis capabilities to include HALO AI and all HALO modules, and to provide centralized access to scientists across the institution. Leveraging Amazon Web Services (AWS), the cloud deployment enables pooling compute resources, auto-scaling, tiered storage and archiving capabilities.

HALO Link, the research image and data management hub for the new cloud deployment, facilitates collaboration between scientists inside and outside of NCI. One of the goals of the project was to integrate the wide range of imaging platforms and data sources across the institute. HALO Link was chosen as the image and data management hub based on its open APIs that provide support for multiple image file formats and facilitate integration with third-party databases. Finally, for clinical trials and diagnostic applications, HALO AP has been implemented for case-management, reporting and quantitative analytics.

Cadila Pharmaceuticals launches Tikacad®

Cadila Pharmaceuticals launches Tikacad® in India, an antiplatelet drug-containing Ticagrelor, a P2Y12 platelet inhibitor indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI).

One in 4 deaths in India are because of CVDs where ischemic heart disease and stroke is responsible for >80% of this burden. [1] Acute coronary syndrome (ACS) is a syndrome (set of signs and symptoms) due to decreased blood flow in the coronary arteries such that part of the heart muscle is unable to function properly or later results into fatality. To reduce this burden, Cadila Pharmaceuticals launched Tikacad® which has shown to reduce stroke incidence by 19% and ischemic stroke by 20%. For at least the first 12 months following ACS, it superior to has shown better results compared to Clopidogrel.

Tikacad is available in the form of 90mg tablets. Tikacad® containing Ticagrelor reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS. Ticagrelor can also be used for the primary prevention of stroke in patients with coronary artery disease as approved by the USFDA.

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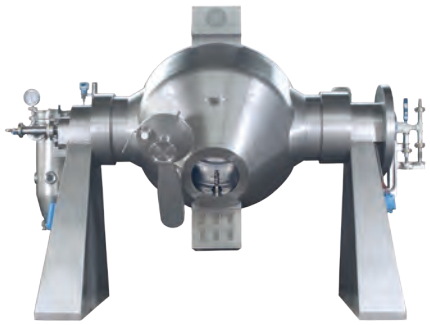

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New Functionality Added to Thermo Scientific SampleManager LIMS software for Manufacturing QA/QC and Contract Laboratories

In response to the data management needs of manufacturing QA/QC and contract laboratories, the latest version of SampleManager Laboratory Information Management System (LIMS) software offers an advanced solution: a built-in electronic lab notebook (ELN), capabilities to streamline operations within contract laboratories and enhanced dashboard configuration for tailored data visualization.

SampleManager LIMS software 12.3 features a fully integrated ELN, simplifying storage, search and retrieval of supplementary information such as unstructured data. As a result, the need for time and resource intensive rework caused by disparate, incomplete and unsearchable data is eliminated, while facilitating improved connectivity and collaboration between laboratories. The ELN adds to the already rich capabilities of the SampleManager LIMS software suite, integrating with the existing LIMS, lab execution system (LES) and scientific data management system (SDMS). Furthermore, the software maximizes process efficiencies within contract laboratories, providing a single system to easily manage customers' work, streamline administrative tasks including pricing and invoicing, and provide customers with a secure, professional portal to log requests and access results.

Importantly, SampleManager LIMS software 12.3 does not require specialized IT personnel to set up dashboards. Instead, the software offers scientists and researchers the option to configure dashboards themselves, to provide user or role views of key performance indicators (KPIs) or other relevant information, allowing for faster, more informed decision making.

Sakura Finetek Europe launches Tissue-Tek SmartConnect®

Caption: Tissue-Tek SmartConnect® the next step in future-proof pathology.

Sakura Finetek Europe launches its latest innovation Tissue-Tek SmartConnect. An automated transfer system that creates a continuous flow between the SMART solutions Tissue-Tek Xpress® x120 Rapid Tissue Processor and Tissue-Tek AutoTEC® a120 Automated Embedding System. This new innovative SMART solution enables a laboratory to optimise their workflow and work more efficient, eliminating repetitive and unnecessary manual work. Hence laboratory technicians can focus more on what matters most: taking care of the best possible patient journey.

Tissue-Tek SmartConnect is the first Sakura Finetek Europe launch from their European research & development department. In the coming months, the first histology laboratory will be equipped with Tissue-Tek SmartConnect to show its value and support the lab technicians in the workplace. ■

"Government Industry Collaboration during Covid-19 and Way Forward for the Industry"

Mr. Satish Reddy, Chairman of Dr. Reddy's and the President of the Indian Pharmaceutical Alliance in conversation with Prof. Arvind Sahay, IIMA

Covid-19 catapulted the world into a grave humanitarian crisis. So far, the pandemic has resulted in a significant contraction in most global economies, high levels of unemployment, unfathomable hardships for contract labor, and most importantly, the loss of one million lives. During these trying times, it is critical for the pharmaceutical sector to continue producing lifesaving medicines and innovate vaccines, drugs and treatment protocols that can potentially save lives.

***Professor Arvind Sahay,** IIMA SIG spoke with **Mr. Satish Reddy,** Chairman of Dr. Reddy's and the President of the Indian Pharmaceutical Alliance on:*

1. *How did the Indian pharmaceutical industry, the relevant industry associations and the Indian Government came together to keep the pharmaceutical sector going at full steam?*
2. *Steps needed to ensure that the industry builds a sustainable advantage in order to not only maintain its position as "pharmacy of the post Covid-19 world" but also enhance it substantively*

Mr Satish Reddy
Chairman of Dr. Reddy's and the
President of the Indian Pharmaceutical Alliance

Prof. Arvind Sahay
Faculty, Marketing Areas, IIM-Ahmedabad

Covid 19 acted as a catalyst to create a mechanism for close cooperation between industry and government, something that needs to be done at scale across industries and government departments.

A. Government Industry Collaboration: Management of the Covid-19 Lockdowns

Though the Government categorized pharmaceutical manufacturing as an essential service and allowed the sector to operate during the lockdown, it faced major disruptions and operational challenges pertaining to availability of raw materials, reagents, manpower and logistics in the initial phases due to some operational aspects missing from the initial Government notifications and the varying interpretations on the ground. .

To mitigate these disruptions, key actions were as follows:

1. Collaborate with control rooms set up by the Department of Pharmaceuticals to streamline, clarify & implement relevant Government notifications on the ground
2. Co-ordinate with central & state government authorities almost "around the clock" to resolve on ground issues in manufacturing operations, logistics, functioning of ancillary industries, etc.
3. Close cooperation between different industry players to effectively manage on ground disruptions and provide real time data flow to the government for better decision making.

Through these collaborative efforts, the Indian Pharmaceutical industry reached near normal level of medicine production by end-May.

B. Reviving the API (Active Pharmaceutical Ingredient) Industry in India:

The percentage of APIs and KSMs (Key Starting Material) that India imports from China has increased from 1% in 1991 to around 60 - 70%, and even 100% for some essential medicines in 2019. This was primarily backed by large-scale manufacturing incentives, supportive R&D ecosystem, liberal policies and cheaper utilities which created sustainable economies of scale for Chinese manufacturers.

The Government of India recognized the need to revive the domestic API manufacturing industry and announced an incentive package worth INR 6,940 Crore on 21 March 2020. The core focus of creating scale and long-term survivability

of the industry was developed through constant engagements between the API and formulation manufacturers and the Government.

The industry was consulted on the finer details of the scheme, namely, list of priority APIs (53 APIS being identified as being particularly critical), levels of incentives, tenure and investment criteria etc. which demonstrates the increase in trust between the Government institutions and the industry. The scheme exhibits the success of multi-department collaboration within the Government from NITI-Aayog to the Department of Pharmaceuticals and Industry in the achievement of a reasonable scheme in a relatively short duration of time.

Industry data is an important yardstick that policymakers use to measure the outcomes of schemes and is a strong feature of the current Government Industry collaboration in the pharmaceutical sector. There does not exist one single source of information which can provide all the data required for policymaking decisions and while the industry plays an important role in filling these information gaps, it would be more efficient to have a neutral think tank that does this job on an ongoing basis. This data backed evidence played a pivotal role in identifying the subsidies and incentives required for domestically setting up API manufacturing plants such that they are competitive globally both in the short as well as long term.

C. The rise of R&D and Innovation in the Indian pharmaceutical industry

The Indian pharmaceutical industry is the world's third largest producer of drugs by volume and is known as the "pharmacy of the world". The future of the industry is dependent on its ability to develop stronger capabilities in innovation & R&D. Apart from the economic benefits of developing innovative products, the Indian pharma sector can contribute to the country through the development of drugs for India-specific ailments that do not get adequate global attention.

Drug discovery in the context of the Indian Pharma sector is still in the early phase. The amendment of the patents Act

On Covid-19 vaccine development and the potential market size: There is a tremendous market potential and India will play a key role since about 50% of the vaccine production globally comes from India and there are several companies who are leaders in this space. There are multiple vaccine candidates from India with some even collaborating with other global leaders in vaccine development.

In the aftermath of Covid 19, detailed roadmap and implementation plans are now in place for API manufacturing and R&D in India.

in 2005 and the increasing involvement of the private sector companies in drug discovery shows that there is a conviction within the industry to step up the R&D and drug discovery in India.

The Government of India has also recognized the importance of R&D and innovation and is currently developing a policy to build innovation capacity both in academia, and in the industry.

The policy is being developed by the Department of Pharmaceuticals in collaboration with industry, academic and policy experts which will address the major bottlenecks with regards to policy, funding, industry-academia linkages, regulatory and infrastructure faced by the R&D ecosystem in India.

The collaborative efforts between the Government, industry and academia in framing the policy central to the R&D ecosystem can create a positive feedback loop which will further galvanize the academia as well as the private sector in their efforts to take India further in the pharmaceutical innovation and R&D space.

D. Future of collaboration between the Government and industry

The collaboration during the Covid-19 pandemic situation whether it was on policymaking, or crisis management, highlighted the trust and confidence that various institutions of the Government displayed in the industry.

Institutionalizing and streamlining this framework for collaboration and setting up neutral agency which can act as a knowledge repository will greatly improve the effectiveness of policymaking in the future.

Academic institutions such as IIMA that have a rich expertise in policy, regulatory as well as industry related areas have the potential to be that neutral agency. A similar framework has been adopted in China such that when it comes to policy decisions, the Government has ready access to data, policy experts from universities and industries and this collaboration has done wonders to the industrial development in China. Such a framework has existed for a long time in USA and Germany – and arguably one reason for the success of these two countries in producing world scale and class pharma firms flows from such an approach. ■

"We believe in not finding customers for our products, but in finding products for our customers."

The global pharma industry is struggling with a huge shortage of high-quality pharmaceutical drugs as well as packaging products. Developing countries face a further threat of low-quality packaging material, as well as cheaper generic drugs being sold to them due to costs. For Rishad, bringing parity to the pharmaceutical packaging industry by providing "best quality for all" products at the same fair price across the globe, has been a key driving force in his key roles in several companies within the KAISHA Group of companies. In an exclusive conversation with PBW, ***Rishad Dadachanji, Director, SCHOTT KAISHA*** *talks about how he has been has been spearheading various projects for his company.*

Rishad Dadachanji
Director, SCHOTT KAISHA

SCHOTT KAISHA is a joint venture with SCHOTT AG - world's leading experts in the production of type-I Borosilicate glass, the gold standard for drug packaging for over a century. Give us an insight into the journey of SCHOTT KAISHA the span of business to what it is today?

SCHOTT KAISHA started as one of the very few Indo-German joint ventures in the country in 2008. What started as an ambitious project with the global pharma glass leader SCHOTT AG, has grown exponentially over the last decade. Our first plant was in Jambusar, Gujarat and I am proud to see the company consistently grow its footprint, with four state-of-the-art facilities across India. All our manufacturing facilities adhere to global standards, and in certain capabilities, more advanced than production sites plants in developed countries. SCHOTT KAISHA produces over 3 billion pharma packaging pieces every year, making it a market leader for quality glass packaging products in India. We cater to the country's top pharma players and some of the leading pharmaceutical giants of the world.

Vaccines, like most injectable drugs, need to be packaged in sterile glass and SCHOTT KAISHA is leading the supply of vials from India. How are you dealing with this challenging demand situation?

Will the Covid-19 vaccines vials require any special handling?

It is a crucial time for the pharma industry as a whole and all of us are doing our best to fight the pandemic. SCHOTT KAISHA is in a strong position to address the expected demand surge due to the Covid-19 vaccines. In fact, we are already supplying to the major vaccine manufacturers and in touch with all our partners to ensure that their existing and future demands for vials are met without any challenges. SCHOTT KAISHA has always been ahead of the curve by expanding its production capacity. This has been our biggest advantage during these unprecedented times- with two of our new manufacturing sites in Umarsadi, Gujarat and Baddi, Himachal Pradesh, we are well equipped to quickly ramp up production as and when more demand arises.

Making these vials was a big business even before Covid-19 appeared in January. How has the industry adopted to the new surge in demand?

Type-1 glass vials are essential for storing highly specialized drug formulations, that are used by all pharmaceutical manufacturers for their complicated medication. This year, the demand for glass vials has increased due to Covid-19 medications as well as its ongoing vaccine

trials. However, the pharmaceutical packaging industry has been extremely forthcoming to ensure that there shall be no shortage for glass vials. SCHOTT KAISHA has been proactively expanding and also introducing new lines in its existing facilities over the past couple of years.

How does SCHOTT KAISHA ensure global quality standards at its plants? What type of machines does SCHOTT KAISHA use?

Our manufacturing sites meet all the global quality standards required to supply to anyone in the world. Our machines are procured from the best suppliers in India and abroad – embodying the sentiment behind Industry 4.0 for automation and smart technology and. For example, we have developed our own cosmetic inspection systems for vials with a French company and this has enabled us to be one of the only companies in the world who can check 100% of the vial surface. We also have our own tool rooms which helps us design and develop our own tooling which is crucial for glass forming.

SCHOTT KAISHA has been known to scale up extremely fast in order to meet customer demands over the past decade, which is also evident from its two new facilities in Umarsadi and Baddi. What are your further expansion plans?

With these two new plants, we are confident that we have enough capacity to cater to any foreseen demand surge for Covid-19 vaccines vials and beyond. Having said that, our manufacturing sites have enough space to introduce more infrastructure in these existing facilities and add more lines and build modules as and when required.

"We believe in not finding customers for our products, but in finding products for our customers." This is a very interesting statement. Could you elucidate further with examples?

Many of our offerings are easily customizable. With our own tool room and design and development teams in place, we can easily develop special and customized packaging as per our customers requirement.

For example, we have recently developed a no-glass-to-glass contact, ready-to-fill vials packaging configuration for one of our customers which could easily get integrated into one of their existing lines with no need of procuring new change parts for the machine. Also, with our ready-to-fill nested cartridges, Car-ter ™, all our customers make use of their existing machines with very minimal change of parts and flow change over time, instead of procuring completely new machines.

Your love for research and innovation led you to take charge a dormant company with no operations. KAISHA LIFESCIENCES born in 2017 started the venture from scratch to introduce a wide range of generic drugs and innovative medication products in the market. Could you give an insight into this story?

When I joined the Group, I was very fascinated by the diversity of our portfolio. Shakai Packaging, now known as Kaisha Packaging, was engaged in the business of manufacturing aluminum seals. It was a small company with a few employees at that time. Apart from being involved in our larger organizations, additionally I took over the responsibility of this company with a goal to bring it up to par with our other companies. It involved revamping the products, upgrading the technologies and building and moving it to a completely new manufacturing site. I am happy to see the company rapidly growing and doing well.

Kaisha Lifesciences was very interesting for me as it not only complemented our Group Companies, but it was also something that my father wanted to build since a long time. So with his blessings and guidance, we started the venture and set up a brand new R&D site along with a new team. As we are now building up our portfolio, we are working with some key multinationals as well as Indian companies on several developments and our product supplies. Thanks to our reputation and trust in the industry, this venture was very well received by our customers and we are looking forward to growing this business further.

Make in India is a major new national program of the Government of India designed to gain momentum for investment, innovation and enhance skill development and build best in class manufacturing in the country. What in your opinion has been the impact of this program?

Make in India is one of the country's biggest industrial initiatives, especially for the pharma industry. India is on its way to achieve its vision of being a global pharmaceutical hub, ensuring high quality, affordable and accessible medicines around the world. Most of the global pharmaceutical players have turned towards India for their supply requirements, giving a further push to the country's pharma sector. In fact, the Honorable Prime Minister Narendra Modi recently assured that India's vaccine production and delivery capacity will be used to help all humanity in fighting the Covid-19 crisis.

With the German partner, SCHOTT AG, SCHOTT KAISHA itself is a great example of foreign investment and Indo-German collaboration in the country. Thanks to the conducive industrial environment in the country, we have also been able to quickly enhance our manufacturing footprint and be a part of the Make in India success story.

With the world under siege and a country wide lockdown due to COVID-19, the lives & economies are going through tough time. Your message for the industry to emerge through this tough time?

This is a very crucial time for us, and the pharmaceutical industry has a huge role to play in reviving our country after the Covid impact. The pandemic has come as a test for all of us, and brings a lesson, to be prepared for future challenges. Companies would have to push themselves to meet the demand in the market, work more proactively and come up with functional, innovative and effective methods to meet unforeseen circumstances. My message would be to stay on the course and recognize the opportunity as well as responsibility that we have to make a sustainable impact in our country's long-term security and growth. ■

ROSS double planetary mixer for wet granulations application

Ross Double Planetary Mixers are well-proven in the manufacture of many vitamin and mineral supplements and to satisfy the requirement of product uniformity and particle size enlargement (granule formation) in the wet massing phase of wet granulations. These machines blend dry ingredients by rotating two identical blades on their own axes as they orbit on a common axis. The stirrers contact virtually every point of the batch and continuously move new materials from the sidewalls to the center of the vessel. As a result, a completely homogenous mixture of the base carrier, vitamins, minerals, botanical extracts, and other nutritional ingredients is achieved in a short period of time.

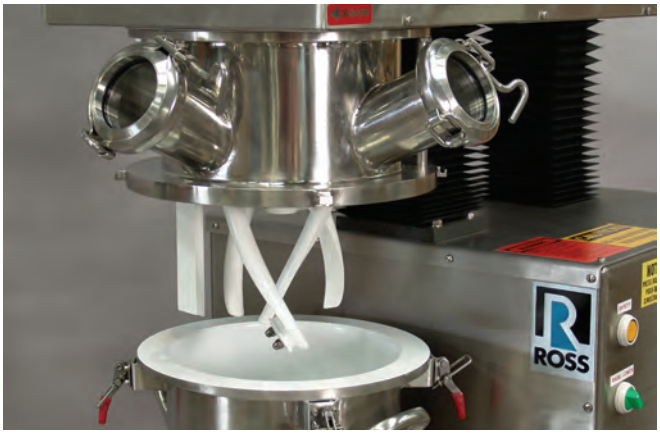
This is followed by spraying an aqueous solution through a multi-nozzle manifold positioned in the hood of the mixer. A metering pump accurately controls the liquid flow rate while the agitated batch transforms into a wet granulated state. One main advantage of the planetary blades is their ability to impart a very thorough mixing action even when the product is dense or not free flowing.

Mixer speed and liquid addition level both influence the size of the granules. A vacuum-capable double planetary mixer with jacketed vessel can be used to dry the granulation under vacuum after the liquid binder/adhesive solution has been added and thoroughly coated on the powders. The mixer layout and design allow for a virtually complete discharge, ensuring high-yield and very minimal product loss.

The final stage of the process is vacuum drying to remove excess moisture from the batch. As heat and vacuum are applied, the stirrers continue to mix the granulation but this time at lower speeds, just enough to ensure uniform temperature while maintaining the size of the granules.

Vitamin manufacturers that have successfully transferred their process from multiple pieces of equipment to a Ross Double Planetary Mixer benefited from significantly shorter cycle times. in addition to simpler handling, cleaning and maintenance, the risks for product contamination and batch-to-batch inconsistencies are also greatly minimized.

Vitamin and mineral supplements in solid



dosage forms undergo mixing, granulation and drying

processes which have traditionally required multiple dedicated pieces of equipment. By combining these operations in a single Double Planetary Mixer designed for gentle blending, thorough granulation and fast drying, manufacturers are able to improve product quality and consistency, reduce processing time and simplify maintenance.

Advantages of Ross Sanitary Double Planetary Mixers

1. **Blade choices.** Three different styles of planetary stirrers are offered: Rectangular Blades, Helical Blades and Finger Blades. The classic Rectangular Blades are commonly used for granulations but the Helical and Finger Blades are also chosen depending on the flow characteristics of a Particular formulation.

2. **Cleanability.** There are no shaft seals, bearings, packing glands and stuffing boxes submerged in the product zone of the Double Planetary Mixer. Agitators are raised and lowered by an air/oil hydraulic lift allowing easy access for cleaning between batches. The discharge valve is flush with the vessel leaving zero “dead spots” where product can stagnate.

3. **Change can design.** This feature further reduces the risk for cross contamination between batches while allowing for semi-continuous operation when one mixer is used with multiple vessels.

4. **Vacuum capability.** Vacuum-rated Double Planetary Mixers offer a fast and reliable method for drying heat-sensitive materials without fear of thermal degradation.

5. **Value-add customizations.** Ross Double Planetary Mixers designed for food- and pharmaceutical-grade granulations can be equipped with a tilted vessel (for convenient discharge), atomizing spray manifold, sealed & purged gearbox, built-in vacuum pump, PLC controls and other customizable features.■

Author

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ITW Chemin launches improved RUST-O-WAX Corrosion Preventive Coating

ITW Chemin launched the improved version of RUST-O-WAX, an aerosol coating for protection of critical metal components against corrosion damage. RUST-O-WAX is a long term outdoor and indoor corrosion protection from rust and corrosion, for machined surfaces and assemblies subjected to long periods of storage or adverse shipping condition. The waxy non-brittle film is highly resistant to humidity and severe corrosive atmosphere.

The new formula of RUST-O-WAX improves its ability to withstand higher temperatures and can be applied directly onto hot surfaces. This translates into long lasting protection, uniform coverage with no sagging during application.

Its features make it suitable for use on moulds used in injection moulding manufacturing process. After prolonged use, the temperature of the mould rises and RUST-O-WAX can be directly applied onto these surfaces for protection prior to storage. In addition to this, RUST-O-WAX is also suitable for protection of finished metal and plastic components, in process parts, battery terminals, farm machinery & metal spare parts against corrosion.

RUST-O-WAX is available in both natural and blue color version aerosol cans of 400 ml capacity. ■

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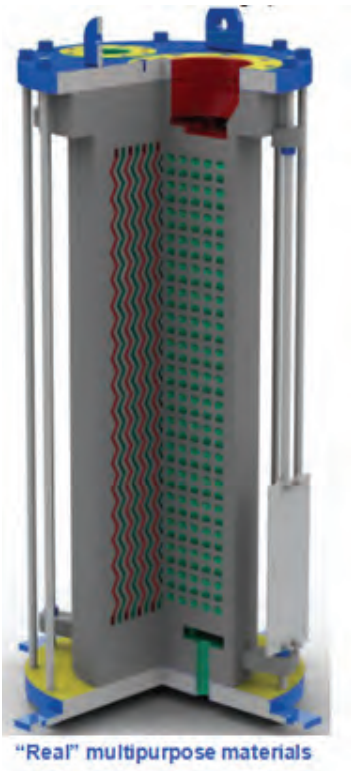
Improved solutions for corrosives processes with graphite technologies

Graphite Technology, a leading global technology company with latest design and improved technology is changing the old and traditional myth of not using graphite condensers in pharma, API, and fine chemical corrosive processes.



"Real" multipurpose materials

Due to several unsolved issues like the **erosion** of graphite blocks, **cracking, swelling** of phenolic resin, etc forced the Indian giant pharma companies to switch to super expensive exotic metal heat exchangers.

For more than two decades the same old cylindrical blocks, mono-block design is practiced and due to poor quality most of the top API companies blacklisted graphite heat exchangers for corrosive API application's.

GT has developed a **"SUPER CONDENSOR"** especially for API, pharmaceutical and fine chemical industry. It's a unique disk type condenser with no metal cylindrical shell around graphite, Ultra-fine graphite grade with less than 5% porosity with a grain size up to 8-5 microns, Temp range (-60/1300) at 20 bar pressure can handle frequent thermal cycles.

"REAL PTFE" Impregnated Graphite; non-sensitive to solvent swelling unlike competitors using graphite with phenolic resin. Non-corroded by most chemical media unlike graphite with phenolic resin of competition. Thionyl chloride, hydrofluoric acid, chlorine can be handled. ■

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Jehan Impex introduces future of swab flocking to combat the spread of COVID-19 in India

India is recently holding the second position in terms of total number of cases of COVID-19. As the efforts towards recovery and 'Unlocking' continues, it has however become extremely crucial to arrest the spread urgently. The healthcare sector and the governments have globally joined hands together to successfully develop a vaccine but meanwhile, there are certain effective methods to combat the spread of COVID-19, one being, swab testing. Jehan Impex is one such company who took a step ahead to become the pioneer in manufacturing of the Swab Flocking machine in India. According to the founder at Jehan Impex, Mr. Atul Mehta- Proprietor said "It took us the first 7 days of the lockdown to transform this year's business only for the swab industry. The idea was not to just provide the flocking machine but an entire assembly with all the raw materials like, non-flock raw swab sticks, flock powder, adhesive, drying machines and more, to be a start to end solution and to ease the process for our clients. "

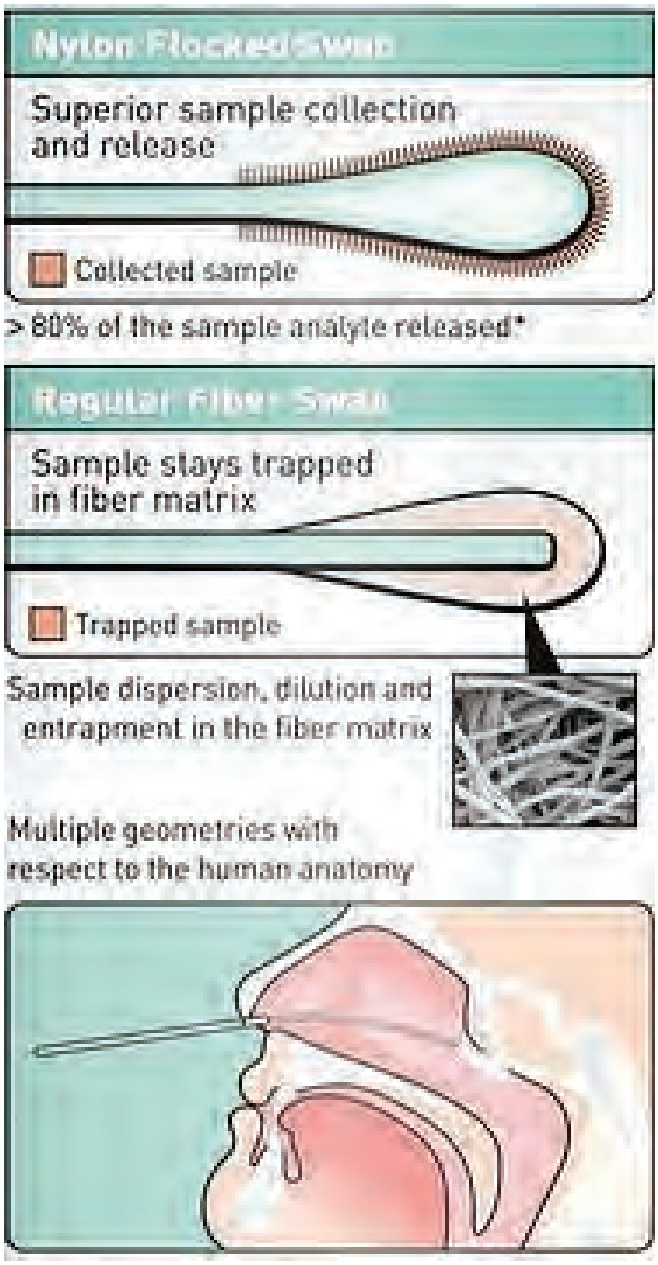
Since the outbreak of COVID-19 gained momentum in India, medical experts have been emphasizing on the importance of aggressive and timely testing for effective containment. Jehan Impex started development and innovation of existing flocking machines in March,2020 with the sole motive of manufacturing a machine that can help to produce flocked swabs in India at a cheaper rate and better quality in comparison with the international market. The commencement of production of flocking machines played a pivotal role in bringing down the cost of the swabs to up to 1/10th of its landing cost, thereby reducing the price of the final kits, as against the kits procured from Chinese companies at a whopping cost earlier. The approximate cost of Jehan Impex machinery is 2-5 Lakhs per unit depending on the model & customization whereas the cost of imported machinery 8-12 lakhs. An estimate of 400 swabs are flocked in 20 seconds which is very promising for conducting mass tests in India. The manufacturing unit is located in Ghatkopar, Mumbai enabling accessibility of sourcing thus, catering to the need of the hour.

Flock swab marks an innovation in

medical swab technology and feature perpendicular Nylon Fibres that provide optimum collection and release of the specimen samples. The flocked technology turns each strand of fiber into a velvet brush-like texture and creates hundreds of contact points for superior collection and release of solid and semi-solid specimen samples.

What Is Electrostatic Flocking?

The Flocking process involves application of short monofilament fibers, usually nylon/rayon directly onto a substrate that has been previously coated with an adhesive. . With the help of a High Voltage generator unit the flock particles are charged causing them to stand erect. The fibers are anchored into the adhesive at right angles to the substrate. The diameter of the individual flock strand is only a few thousandths of a centimeter and ranges in length from 0.05 to 5mm.



Flocking Swabs By Art-O-Flock™ Electrostatic Flocking Machine

Flocking is a 3 step process which includes;

- **STEP 1: Application of adhesive** Adhesive is applied to the medical swabs.
- **STEP 2: Flocking -** The Jig fixer affixed with swabs is placed in the ART-O-FLOCK™ Flocking chamber. The flocking machine is turned on and in just 20 seconds 400 swabs are flocked.
- **STEP 3: Drying -** The flocked swabs are kept in the rack for drying.

Advantages of flocking with ART-O-FLOCK™ Flocking machine;

- Manufactured at 1/10 the price of the imported swab

- Almost 7x the output as compared to the other similar machines.
- 99% usage of raw material
- Extremely quick production with 400 swabs in 20 seconds
- 100% accurate and even Flocking is achieved
- Power consumption is just 80 Watts whereas the other machines consume appx. 400-500 watts
- Machine can be operated 24x7 without any heating.

Electrostatically Flocked Swabs

WHAT ARE FLOCKED SWABS?

Flocked Swabs utilize innovative Nylon fiber technology under condition of electro-static field. Flocked Swabs feature perpendicular Nylon Fibers that optimize the specimen collection and release.

ADVANTAGES OF FLOCKED SWABS:

1. **ENHANCED SPECIMEN RECOVERY**- The flocked technology turns each strand of fiber into a velvet brush-like texture and creates hundreds of contact points for superior collection and release of solid and semi-solid specimen samples.
2. **HIGH LIQUID ABSORBENCY -** Strong capillary hydraulics between the Nylon strands draw up maximum liquid sample.
3. **OPTIMUM SAMPLING -** Flocked Swabs are an excellent choice for use with rapid diagnostic tests because of their efficiently of collecting cells or organisms at the collection site and rapid release of entire cells.
4. **RAPID ELUTION -** Flocked Swabs contain no inner fabric or other inner core to absorb the specimen. Hence a larger amount of specimen is collected and retained. Not only does this provide for better sample yield, it also allows a more rapid and complete release of the sample into liquid media.

Jehan Impex has been providing its machinery and raw materials to key pharmaceutical companies such as HiMedia Laboratories Pvt. Ltd., Micromaster Laboratories Pvt. Ltd., Suparshva Swab (I), CML Biotech Pvt. Ltd., Bhat Biotech Pvt. Ltd., Levram Lifesciences Pvt. Ltd, etc. Mass testing is key to fight the Corona Virus in India, and Jehan Impex has delivered a highly cost-effective solution, consistent in quality, flocking machines that would now help manufactures to produce/launch the world's most affordable and effective COVID-19 Testing Kits. ■

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New mobile table series for lab devices withstands large mechanical loads

Sonation
Active Pump Protection System

Many pharma and biotech companies today have either not digitized their production processes or only to a certain extent. If production data is available electronically at all, it is hardly contextualized, so that it can only be used insufficiently to increase production performance, quality or compliance. In most cases, it is challenging to setup upfront clear, reliable and executable digital production IT strategies, where all necessary aspects in terms of people, processes, data and technology are carefully considered, planned and put into a context to drive production IT compliance and excellence.

The new Principal Consulting & Client Advisory services help drug manufacturers to develop and implement holistic digital manufacturing IT strategies utilizing the broad portfolio of Werum Solutions, that is tailor-made to the customer's circumstances and business targets. Customers will be advised and supported throughout the entire digitization lifecycle, from the very beginning of the digital strategic analysis and definition process to project/program execution up to optimization potentials in operations. The new unit is headed by Zinaid Dzinovic, who worked for several years at a major pharma and biotech manufacturer in Switzerland in various positions.

"Turning pains into gains: with our new Consulting & Advisory services we address our customers' key pain points in business, quality, compliance and operational excellence," says Zinaid Dzinovic, Director of Principal Consulting & Client Advisory Software, Körber Business Area Pharma. "The new services are complementing our existing Werum Solutions consulting portfolio and help our customers in the strategic process towards fully digitizing their pharma operations."

Torsten Isenberg, Vice President Global Business Consulting Software, Körber Business Area Pharma, adds: "In discussions with our customers, we often find that the organizations are only insufficiently prepared for the digital transformation. We want to ensure an understanding for the disruptive potential of digitization. Together with our customers we develop and implement the right strategy for the successful journey to their digital pharma 4.0 factory of the future." ■

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Fully Automatic advanced vertical Autoclave with pre and post pulsing

Autoclave/Steam sterilizers are used in a various Avenues Like Hospital, Pharma and institution for sterilization Purpose. They are commonly used to sterilize pharmaceutical, surgical, and laboratory items. A basic autoclave uses the power of steam to kill bacteria, spores, and germs that may be resistant to boiling water and powerful chemicals.

Steam sterilization is inexpensive, nontoxic, effective, and rapidly heats most materials, including penetrating fabrics. The basic principle of steam sterilization is to expose each item to direct steam contact at the required temperature and pressure for the specified time. There are four parameters of steam sterilization: steam, pressure, temperature, and time. The most common steam-sterilizing temperatures are 121°C and 134°C. These temperatures should be maintained for a set period for the microorganisms to be killed.

Autoclaves are critical components in ensuring consumer safety. Without validation and proper mapping, your autoclave may not be operating correctly, which puts people at risk. Validation of your autoclave cycles with NIST-traceable data loggers is recommended and often required by regulating bodies to ensure proper sterilization.

The high degree level of sterilization depends on the latest protocol incorporations like Air Removal ,Pre and post Pulsing with efficient Vacuum Pump ,Fully Automatic with advanced PLC and Touch Screen HMI, Recording and Logging of current Data's With Real time through Printer, Password protection at more level and Fulfilling the Requirement of 21CFR Part 11.

These Fully Automatic Vertical Autoclave has got a gentle single turn door closing and opening Mechanism with pressure lock safety device. The top lid and

other four sides are enclosed with SS panel which protects internal gadgets and serve best heat insulations During operations. Equipment can be moved anywhere and doesn't require any Fixed Water inlet and Drain Connection

Automatic water intake mechanism with alarm fulfil the thirst of Autoclaves and never interrupt the sterilization cycle. There are many programmes for different recipes like Gravity, Pre-vacuum, Express - 134 oC cycle, Liquid for fluid inside bottles, Latex, Leak test and Bowie Dick. Where the parameters can be altered as per User requirement.

There are two options regarding Single or Double walled construction ,Separate Boiler supply the steam and hold steam for next consecutive cycle with minimising the time. Which plays a vital role during dry sterilization.

The capacity Varies from 35 to 200 Litres the operating Voltage from 230V Single phase to 440V 3phase.Door Sealing is done by a special design Silicone Pharmaceutical Grade Epochal Type Gasket. The Material of construction all wetted parts are made of SS316 material and Remaining SS304. ■

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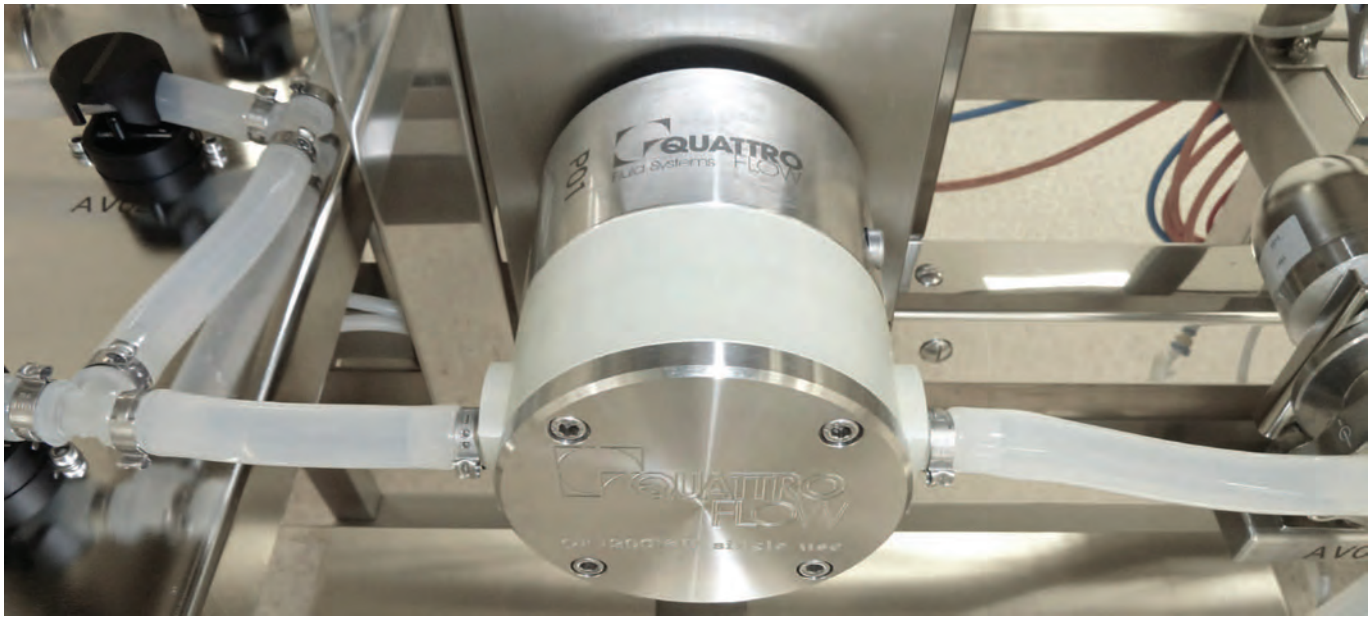
Single-use Pumping Solutions



The development of single-use quaternary diaphragm pumps has been an undoubted boon for the manufacturers of biopharmaceuticals. The image above shows a standard plastic pump chamber. The next step in this evolution with the creation of a pump chamber replacing system from Quattroflow™ that optimizes time, cost, reliability and safety.

When attempting to describe the processes that are inherent to biopharmaceutical manufacturing, words like “complex,” “precise” and” pure” come to mind most often. That being said, the importance of those terms would appear to make words like “fast” and “quick” incompatible with the production of biopharmaceuticals. However, that is not necessarily the case. You see, the most successful biopharmaceutical manufacturers are those that can reliably produce important drugs that are safe for human use while also getting them to market in a timely manner that maximizes the earning potential of patent windows.

This is where pumps become a critical part of the equation. Today’s most common biopharmaceutical-manufacturing systems require the handling, transferring, processing and purification of large-molecule drugs produced in living organisms like animal-cell cultures, bacterial cells or yeast. This must be done in a liquid phase with the handling of these materials performed by pump technologies that can reliably provide volumetric consistency and accuracy,

pressures and flow rates, and low-pulsation, which are required in the process, and low-shear, low-heat input and material compatibility that protects the biological drug from being harmed .

In general, the manufacturing process is separated in two main stages: The first is upstream processing, in which genetically modified cells suspended in liquid culture media are grown in bioreactors to produce the desired product. The second stage is the separation and purification of the target molecule from the cells and byproducts, which is ca lied downstream processing. Traditionally, permanent stainless steel pumping and processing systems have been used for these operations, but the time and cost needed to operate, clean , maintain and quality control the system before the next production run could commence became prohibitive.

That led to a true innovation for the industry, the creation of single-use pumps that feature a disposable pump head and chamber that can be easily removed and re placed between production runs, eliminating the time and cost needed to revalidate the equipment in a stain less-steel system. While single-use pumps have been an undoubted boon to biopharmaceutical manufacturers - with positive displacement quaternary (four-piston) diaphragm pumps becoming a go-to technology choice for many manufacturers - there were still improvements that could be made in optimizing their changeover times and simplifying the installation process. A breakthrough in this area came with the development of a pump-chamber replacing system that reduces the time needed to replace a disposable single-use pump chamber to mere seconds.

First, we should take a step back and give some context to just how significant “complex,” “precise” and “pure” are to the biopharmaceutical-manufacturing process. The foundation of biopharmaceutical manufacturing rests on various types of unit operations. While each unit operation features its own set of operational criteria, they are alike in that they can only produce a viable, contaminant-free drug suitable for human administration if the manufacturer strictly adheres to an unbending set of operational parameters and structures.

Here’s an overview of the more common unit operations in biopharmaceutical manufacturing:

Also known as cross-flow filtration, in this process the biopharmaceutical’s feed stream flows tangentially across the filter membrane at positive pressure. As it passes across the membrane, the portion of the feed stream’s molecules that are smaller than the membrane’s pore size pass through the membrane.

Objective	To pllifytargetmole CIJlesfrom the othe rprocess stream through adsorptio nto a resin immo olized in the chromatogr ap column.	To remove potential virus particles that may contaminate the product.	Product concentration and/or buffer exchange.
Challenge	Chromatography columns contain expensive media that make proper feeding of the resin and maximum separation efficiency very important.	Most virus-filtration systems run at a constant pressure, but when the filter clogs, the flow rates decrease and not in a linear fashion. This adversely affects the performance of the filter, product yield and overall quality.	Maintaining cross-flow over the membrane and trans-membrane pressure (TMP) at the same time.
Required Pump Capabilities	Constant flow rates that can operate in conjunction with varying pump pressures optimize chromatography processes.	Pumps that combine a high turndown ratio with minimal pulsation improve performance in virus filtration.	Low pulsation flow decreases fluctuation in recirculation and trans-membrane pressure. In addition, low heat generation and low shear stress to the product.

TFF is different from what is known as normal-flow (NFF), or "dead-end," filtration, in which the feed flows entirely through the filter membrane with the size of the pores determining which portion of the feed is allowed to pass through and which will remain trapped in the filter membrane. TFF also differs from NFF because the tangential motion of the fluid across the membrane causes any trapped molecules to be "rubbed" off, which eliminates the formation of a gel layer that would lead to blocking of the membrane. This mode of operation means that a TFF process can operate

Single-use quaternary diaphragm pumps from Quattroflow™ are becoming increasingly popular for use in the most common unit operations in the manufacturer of biopharmaceutical drugs. That's because the single-use pump's replaceable heads and chambers significantly reduce the time needed for cleaning and quality control between production runs.

with relatively high product-load without any fouling (blocking) of the filter. Typically, a membrane pore size is selected that retracts the target molecule in the so-called retentate. The portion of small molecules, including water, that will pass the membrane is called permeate. The result is a high concentration of the target molecules in the retentate.

While TFF is used to concentrate the product based on the molecule size, chromatography is a process that is used to purify target molecules from the other process stream based on adsorption to a resin. This resin is compressed and immobilized in a so-called chromatography column. When the product is pumped through this column, the target molecule can bind (adsorb) under specific conditions at the chromatography resin, while contaminants either do not adsorb or can be washed off. By changing the conditions again (e.g. pH level or conductivity) the target molecules will be released (eluted) from the resin and collected separately from the other process stream to achieve a purified product. Chromatography columns contain expensive media that need careful handling. Protein A resin, for example, can cost many thousands of dollars an ounce, making proper feeding of the resin extremely important. In this application, pumps are used to pack the resin into the chromatography column and then pump the biopharmaceutical material through the column. Both are critical operations that require a high, constant flow rate and pressure.

These systems are used to ensure the safety of the drugs that are produced. They do this through the removal of potential virus particles via constant pumping pressures with variable flow

THE ADVANTAGES OF SINGLE-USE PUMPING SYSTEMS HAVE BEEN TAKEN TO AN EVEN HIGHER LEVEL WITH THE CREATION OF A PUMP-CHAMBER REPLACING SYSTEM THAT SIGNIFICANTLY LOWERS CHANGE OUT TIMES

The EZ-Set Pump Chamber Replacing System from Quattroflow™ allows single-use quaternary diaphragm pump chambers to be replaced in as little as 30 seconds without the need for special tools or torque wrenches. The result is decreased downtime during product changeovers and an improved production process.

rates. Most typical virus-filtration systems run at a constant pressure due to the nature of the tight pores in the filtering medium, but the flow rates will decrease as the filter's pores become fouled. When this happens, the flow rate will not decrease in a linear fashion, which will adversely affect the performance of the filter, product yield and overall quality. To combat this phenomenon, pumps that combine a high turndown ratio with minimal pulsation in the pumped fluid are used.

The common thread between these various types of unit operations is their need for and use of a pumping technology that can satisfy their specific operational parameters. Again, these unit operations are process in which the quaternary diaphragm pump excels, while competitive technologies, such as peristaltic (hose), lobe, centrifugal and piston pumps, may struggle to meet a series of strict product-handling and -transfer requirements.

Some additional mention must also be given to the advantages that utilizing single-use quaternary diaphragm pumps in biopharmaceutical manufacturing can deliver. The main advantage for these pumps - whether used in traditional stainless-steel or

single-use setups - are their unique form of operation: The four quaternary diaphragms are driven one after another by a connector plate, which moves back and forth out of its central position in a stroke that is gene rated by an eccentric shaft, with the length of the stroke determined by the angle of the eccentricity. The four pumping chambers, which actually operate in the same way the human heart does, keep the product flow constantly moving forward in a volumetrically consistent low-shear and low-pulse manner.

The pump's chambers also contain no rotating parts that can be subject to friction, meaning that there is minim um heat buildup that can compromise the product. This mode of operation means that the pumps can run dry, are self-priming, and produce minimal shear because of low slip. In addition, they offer low-pulsation, leak-free operation while having great dry/ wet suction-lift capabilities.

This turndown capability and range for quaternary diaphragm pumps is also unique in the biopharmaceutical industry. As the products go from development to clinical trials and then to commercialization, proper scale-up is essential. In other words, the same pump in a lab may need to handle flow rates as low as 1/2-ounce per minute while also being able to deliver commercial production flow rates of 50 gallons per minute or more.

The quaternary diaphragm pump is also easily adaptable to single-use production configurations. A single-use pump enables biopharmaceutical manufacturers to essentially eliminate the often times prohibitive cost of cleaning and validating their pumps and systems. The result is a quicler and most cost effective production process and one that still delivers preferred levels of product purity and sterility with no chance for cross-batch or cross-product contamination.

The fulcrum of the single use pump is its product-wetted plastic pump chamber that can be replaced as a complete unit.

The Next Step Forward

So, now we arrive at the next step in the evolution of the single-use quaternary diaphragm pump that is used in unit operations within biopharmaceutical manufacturing. While single-use pump technology conquered the question of how to reduce cleaning and revalidation time and costs after production runs, there was still more ground that could be plowed in the realm of reducing the time needed for pump head replacement.

The breakthrough came with the development and release of the pump-chamber replacing system, namely the EZ-set model that was created by QuattroflowTM, Duisburg, Germany a product brand of PSGs, Oakbrook

Terrace, IL, USA, a Dover Company. The system reduces downtime in the production-changeover process. It allows manufacturers to replace a single-use pump chamber in 30 seconds or less without the need of torque wrenches, or other special tools and equipment – all while allowing the user to be able to wear rubber gloves during the replacement process. Pump-chamber replacing systems can also be retrofitted on existing motor drives, which also makes upgrades quick and easy to perform.

Replacing the pump chamber requires just five simple steps:

- Remove the pump's pressure plate
- Take the pump chamber out of the ring drive
- Push the new pump chamber onto the ring drive
- Reinstall the pressure plate
- Slightly rotate the pressure plate to lock.

In fact, the pressure plate is so simple and easy to dial in, that no physical strength is required, menaing that everyone from a kindergartner to a weightlifter can install the pressure plate.

Conclusion:

Many skills are needed to produce biopharmaceuticals, but in the end the final product must be one that is unquestionable safe to use while simultaneously allowing the manufacturer to reap the financial benefits of an optimized patent window. The arrival of single-use pumps on the scene has virtually eliminated the cost and downtime that were previously required to clean and validate pumping systems. A further leap ahead has been taken, however with the creation of the pump chamber replacing system, an innovation that will continue to optimize time, cost, reliability and safety capabilities in the ultra-important biopharmaceutical-manufacturing

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Dr. Andreas Frerix is the Product Manager for Quattroflow™ pumps. Dr. Frerix can be reached at +49 2065 89205 39 or andreas.frerix@psgdover.com. Based in Duisburg, Germany, Quattroflow offers a full line of positive displacement multi-use and single-use quaternary (four-piston) diaphragm pumps and accessories for use in the biotech, food-and-beverage, personal-care and nutrition industries. Quattroflow is a product brand of PSG®, a Dover company, Oakbrook Terrace, IL, USA. PSG is comprised of several leading pump brands, including Abaque®, All-Flo, Almatec®, Blackmer®, Ebsray®, EnviroGear®, Griswold™, Mouvex®, Neptune™, Quattroflow™, RedScrew™ and Wilden®.

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Future of Work:
Building the new commercial operating model

The healthcare eco-system today is navigating unchartered territory with COVID-19 impacting all major stakeholders. Due to the unprecedented nature of the pandemic, traditional channels of interaction between patients, prescribers, healthcare companies and pharmacies have been disrupted, as depicted in Exhibit 1.

With no imminent respite, innovative and immediate measures have been taken across the eco-system to combat these new challenges. The results of a BCG survey of 200 physicians across specialties in metro and tier 1 cities indicate that 84 percent respondents have moved to teleconsultations during the lockdown. This emerging trend has also benefited existing teleconsultation platforms such as Practo, Mfine and Lybrate. Patients too have moved online, with leading e-pharmacies witnessing a 100-200 percent growth in orders since the lockdown.

Healthcare companies, meanwhile, have focused on supporting prescribers and patients in new ways, while safeguarding employees and upskilling them to operate in a changing environment. Results from the physician survey indicate that 98 percent prescribers spent time on digital mediums such as webinars organized by leading healthcare companies. Additionally, all prescribers that participated in our survey were contacted through phone / video by multiple healthcare companies. Firms have also embraced the digital way of executing internal processes and are focused on capability building of their field force.

While healthcare companies have successfully identified and responded to the immediate needs, they recognize the need to rethink and redesign their commercial operating model for the future. This article provides BCG's view on the 4 key questions that companies need to answer in order to design their future commercial operating model.

- What are the elements that will ensure prescriber pull for digital engagement?

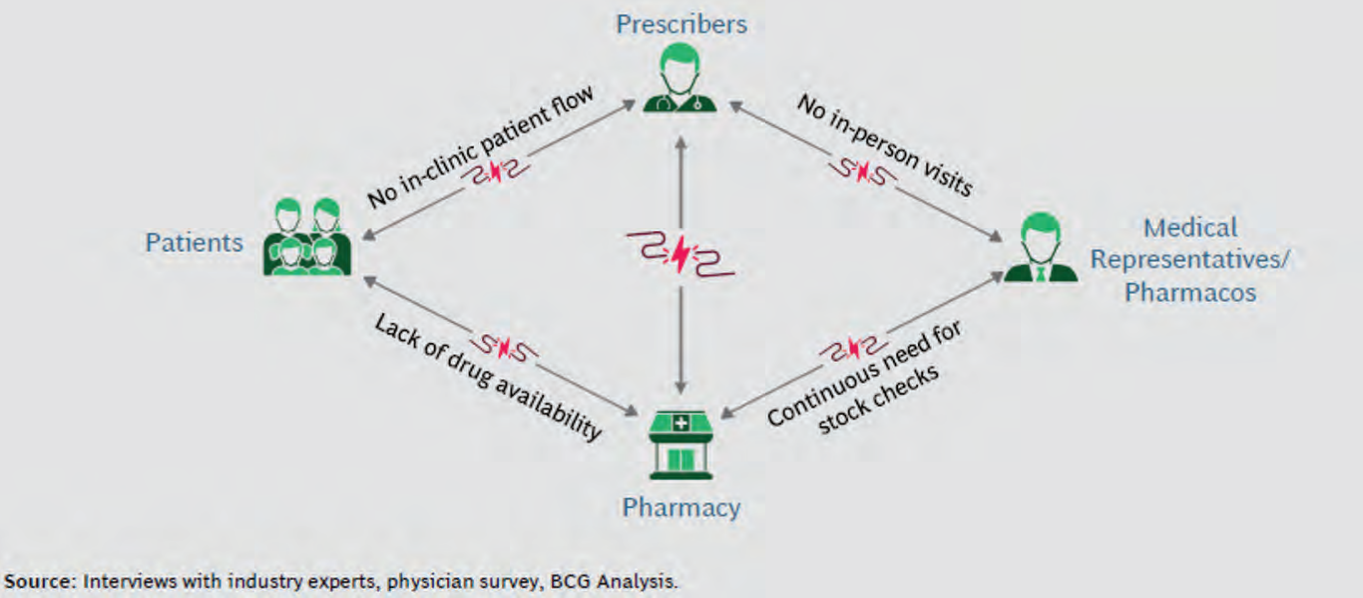


EXHIBIT 1 | Disruptions in The Pharma Eco-System During the Pandemic

- How should the new sales call be designed?
- How should companies enhance their direct connect with patients?
- What will the commercial organization of the future look like?

Digital Engagement Platforms

According to our physician survey, 61 percent prescribers found the various digital engagements conducted by healthcare companies during lockdown to be effective, and 70 percent indicated that they would like to continue the same going forward. 64 percent of this set intends to spend 30 mins-2 hours per day on these platforms.

With restricted access becoming the new normal, it is imperative for healthcare companies to engage with prescribers through digital avenues. As displayed in Exhibit 2, apart from scientific webinars, prescribers find multiple other mediums effective for engagement. These include online group discussions, patient case studies, sessions with KOLs (Key opinion leaders) etc. Companies can explore these mediums going forward. However, in order to make the engagement effective and value accretive it is imperative that across each medium, companies develop high quality and differentiated content. Additionally, one should ensure that platforms are both easy to use and access.

Healthcare companies, in our view, can potentially explore four different models as they pursue a sustainable digital engagement channel with prescribers. They can continue with the current model of curated webinars and e-mail marketing, or progress to a level which involves online

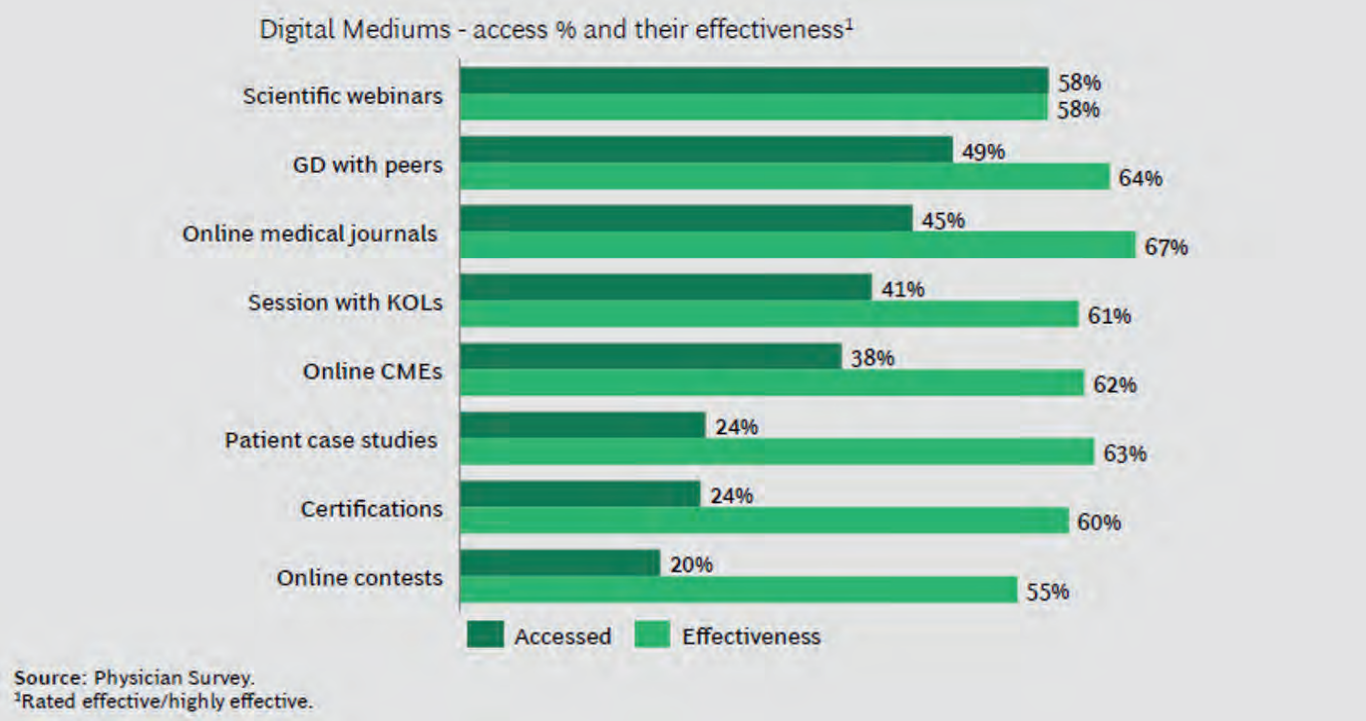
certifications from reputed associations. Awarding of credit hours through these certifications / courses can be explored, thereby increasing user loyalty. Additionally, companies can explore engaging with prescribers through an integrated patient consultation platform. These platforms should aim to alleviate key issues faced by prescribers in diagnosing accurately and providing prescriptions to patients. The most comprehensive choice for companies is to offer prescribers a versatile platform offering variety of content and engagement across multiple channels (webinars, online CMEs, online group discussions etc.), something that can be referred to as NETFLIX for the Rxer (Exhibit 3).

There are certain implications for a firm across each choice / level of engagement. To set up and run NETFLIX for the Rxer, companies will first need to develop partnerships for content, which will require frequent refreshes. Firms will also need to enable personalized recommendations for prescribers basis platform usage to ensure good customer experience.

New Sales Call

As mentioned earlier, sales teams have proactively maintained their relationships with prescribers through whatsapp / phone calls. Prescriber feedback on this mode of engagement, however, has been mixed (Exhibit 4). According to our survey, 50 per cent prescribers (both GP / CP and

EXHIBIT 2 | Digital Mediums - Access % and their Effectiveness



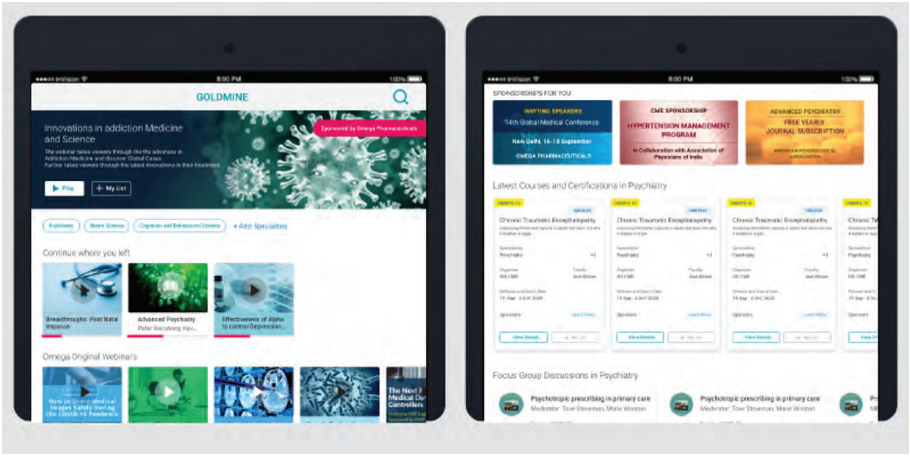


Exhibit 3 | NETFLIX for the Rxer: Our Vision

specialists) currently don't find this form of detailing effective. The major issues cited included a) poor field force communication during digital calls b) higher duration of phone calls and c) no scheduled time being set for digital calls. However, interestingly, 60 percent prescribers are likely to continue with virtual interactions.

In our view, it is imperative for firms to effectively adopt this model considering that the prevailing environment is unlikely to change in the near-term. ~68 percent prescribers are likely to curtail field force visits post the lockdown, with a majority restricting visits to once a month—a sharp decline from a frequency of 2 or more times in a month pre-COVID. Healthcare companies will now need to complement their physical reach models with virtual in-teractions to ensure that similar levels of engagement are maintained.

Companies can move from their current model of detailing via whatsapp / phone calls to centralized push messaging comprising consistent, repeated delivery of company / brand and scientific information. Alternatively, companies can progress to detailing via video conference—similar to an in-person call. An advanced level would be the adoption of an e-detailing platform. These platforms allow medical representatives to stream brand related content on a video call while being visible on the video link to respond to any questions. This can be executed at a time convenient to the physician. This has been depicted in Exhibit 5.

Achieving success in e-detailing will require differentiated content and delivery compared to in-person detailing. Scientific content interspersed with brand details can increase engagement. Training of field force on effective communication through digital channels will ensure consistent delivery and messaging.

Incorporation of this platform would require healthcare companies to develop partnerships and generate content specific to this medium, customized at a prescriber level. Once initial pilots have been completed, firms would need to embed these calls into the sales cycle, across

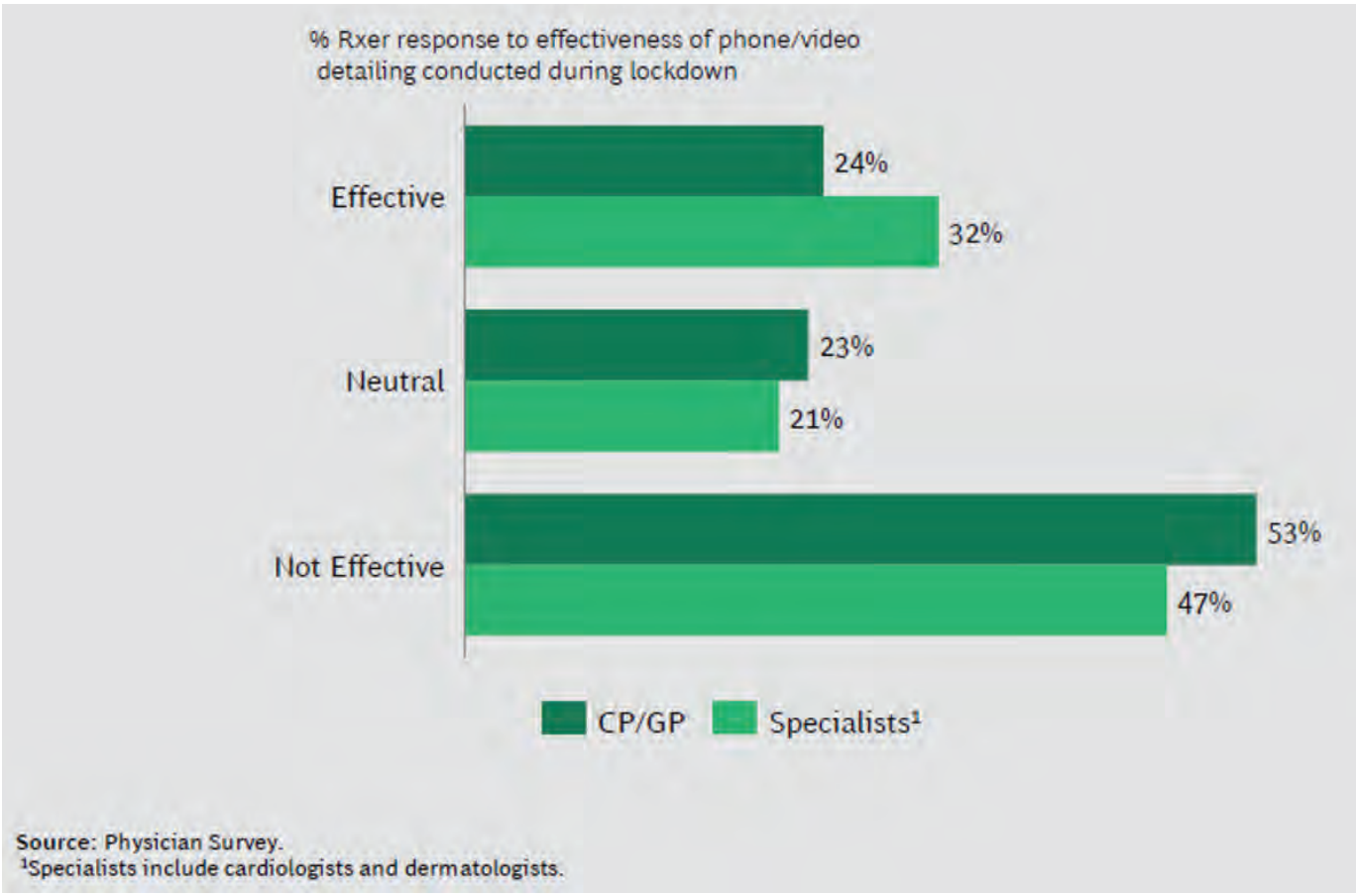


EXHIBIT 4 | % Rxer Response to Effectiveness of Phone / Video Detailing Conducted During Lockdown

planning, execution, review and coaching.

Direct Patient Connect

The rise of e-pharmacies and teleconsultations during COVID-19 has made it easier for healthcare companies to access patient pools. In our view, companies can engage directly with patients by enabling patient services for existing patients or developing therapy shaping initiatives for new patients.

Enabling patient services should be designed keeping in mind key patient pain points across treatment and adherence of therapy. Therapy shaping initiatives, on the other hand, are devised to drive mass scale awareness and improvements in diagnosis rate thereby facilitating access to new patients. Exhibit 6 below details the same for COPD (Chronic obstructive pulmonary disease)

To become a leader in therapy shaping, the selection of therapy plays a very important role. Healthcare companies that enjoy a leadership position in TAs (therapy areas) should prioritize diseases that have a low diagnosis rate. A separate marketing team

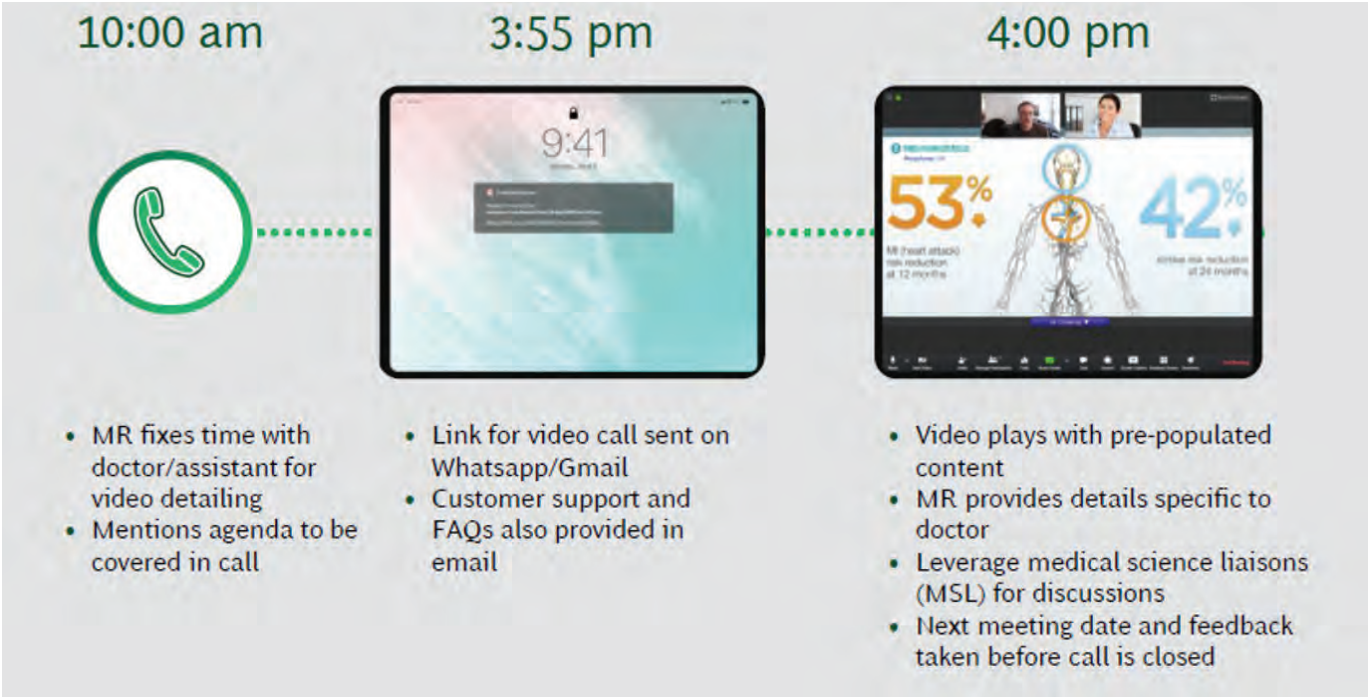


EXHIBIT 5 | E-Detailing Platform: Our Vision

may be established for this purpose.

Commercial Org of the Future

In our view, adoption of digital mediums by healthcare companies in internal meetings and reviews can be sustained even post the lockdown. In addition to current changes, firms can leverage digital to enhance the effectiveness of managers by using tools such as automated root cause analysis, execution alerts etc. Further, healthcare companies can develop a differentiated coverage model by doctor segment and contribution i.e. KOLs, frequent prescribers and erratic / non prescribers (Exhibit 7).

Adoption of such a coverage model will free up time available with the field force. This can be utilized to increase coverage amongst the non-prescribing doctors and strengthen relationships with channel partners.

At the same time, adoption will require an augmentation of current capabilities. Companies will need to focus on creating a digital COE (centre of excellence) that refreshes content. Apart from this, lead roles across E-SFE and digital marketing will need to be created. Firms can also consider establishing a team of medical liaisons to coordinate with partners and strengthen relationships with KOLs. Investments will need to be made in data and analytics, with initiatives towards data security and data management to protect privacy of all stakeholders as usage

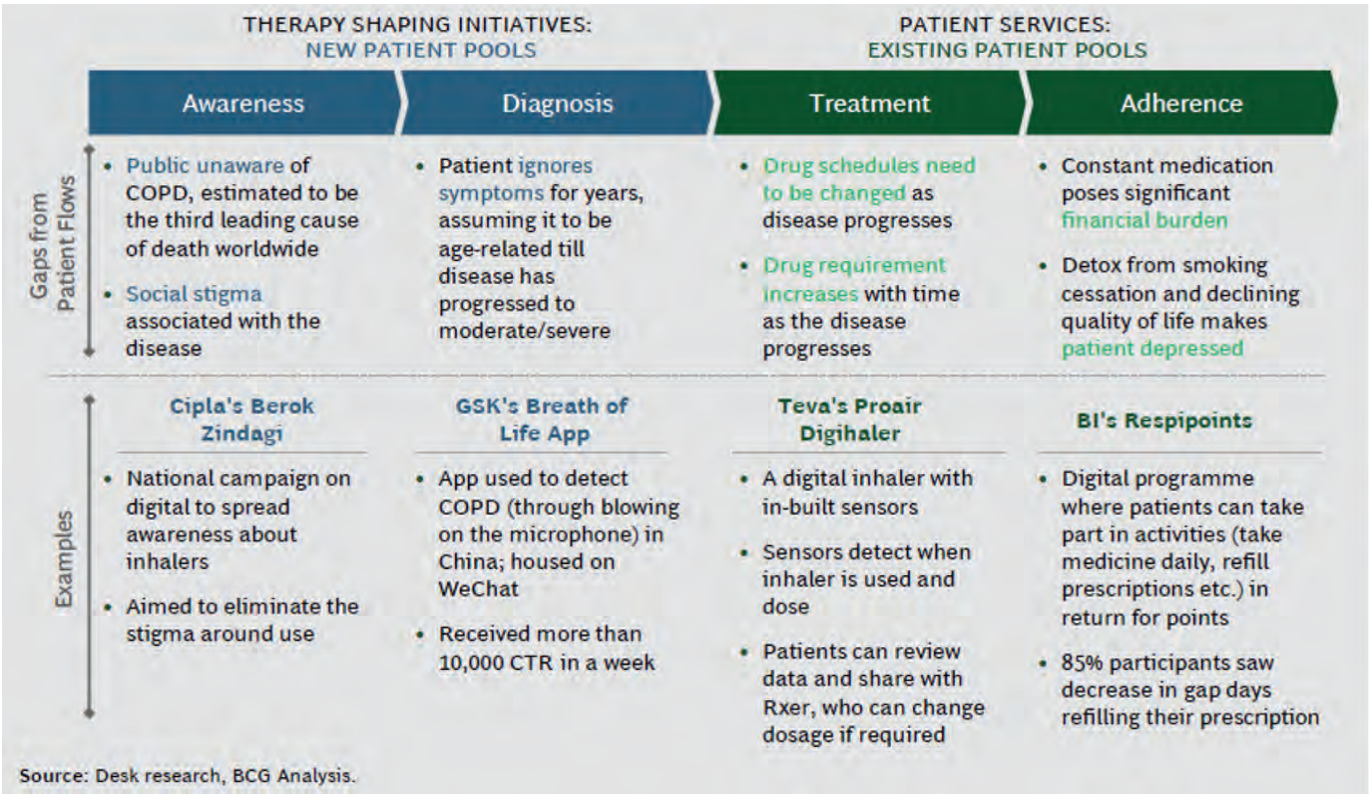


EXHIBIT 6 | Therapy Shaping Initiatives and Patient Services

expands.

SUMMARY

The journey towards "Future of Work" is defined through a maturity model across the elements of digital en-gagement platforms, new sales call, direct patient connect and commercial organization of the future. A summary view has been depicted in Exhibit 8.

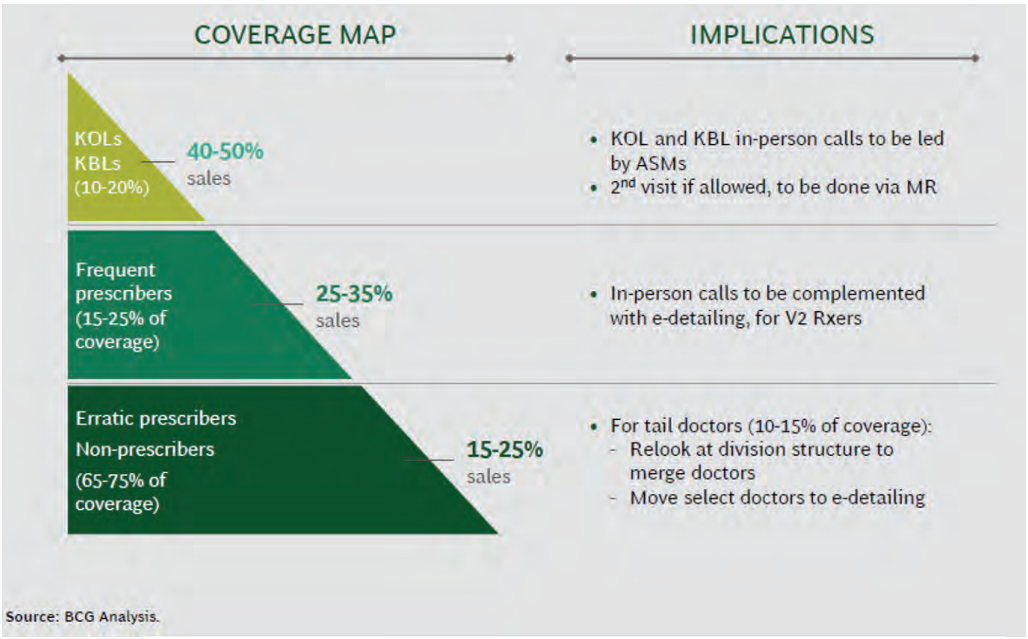


EXHIBIT 7 | Commercial Org of the Feature : Differentiated Coverage Model

Healthcare companies can view the above as a chessboard and decide where they

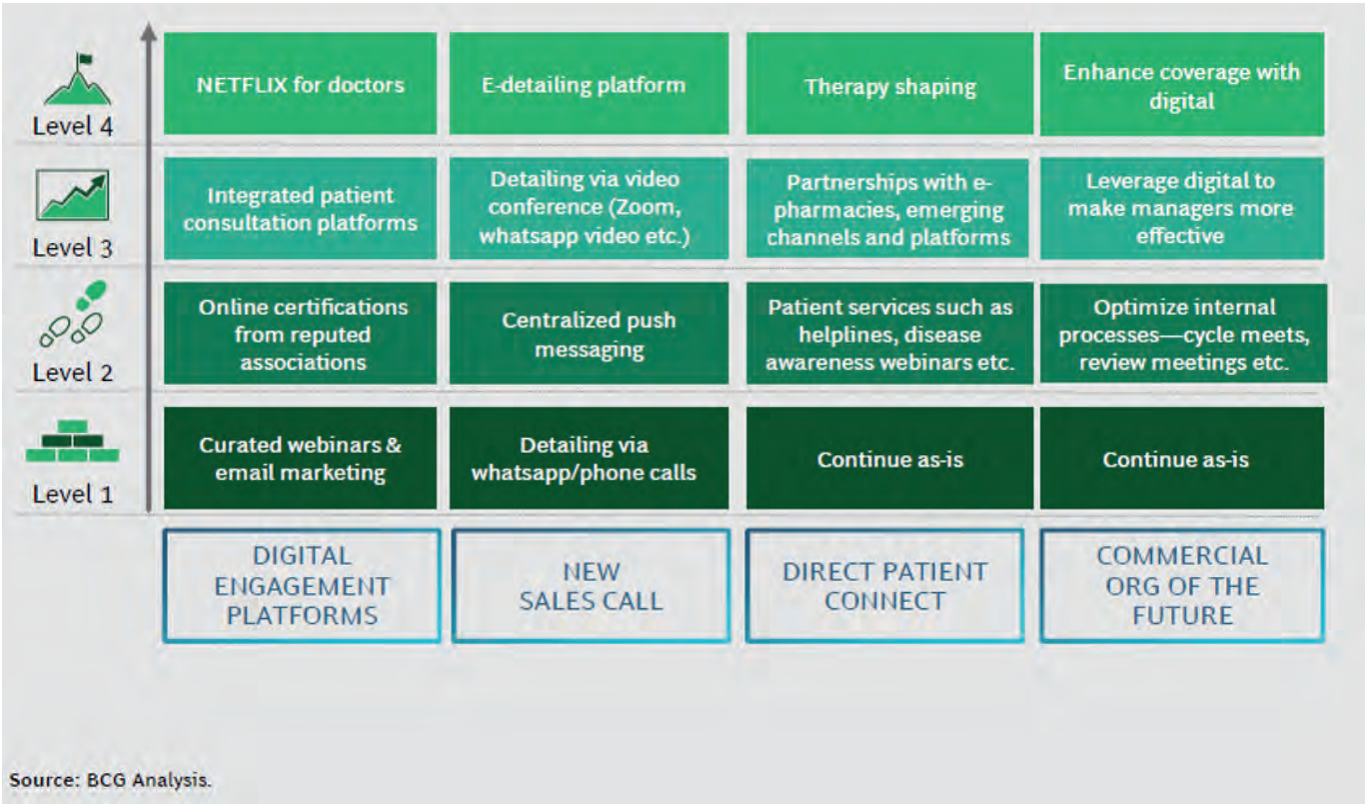


EXHIBIT 8 | Summary

want to play basis their strategy, prescriber preferences and investment willingness. For each choice, there are implications on the firm's commercial operating model, with focus required on building new capabilities.

Benefits will be visible through increased field force productivity and optimization of sales and marketing costs. Adoption of Level 4 across elements can result in an improvement of 5-6 percent in field force productivity, with a 4-5 percent optimization in S&M costs. ■

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X-Ray Crystallography: A Revolutionary Tool in the Study of Solid Forms of Pharmaceuticals

X-ray crystallography is a powerful non-destructive technique for determining the molecular structure of a crystal and finding out how particles are arranged inside crystals. X-ray crystallography uses the principles of X-ray diffraction to analyze the sample, it is done in many different directions so that the 2D and 3D structures can be built up. It is a technique that has helped to deduce the 3D crystal structure of many materials, especially biological materials and revolutionized the field of solid state chemistry, especially in pharmaceutical landscape. William Bragg (father-son duo with same name), invented X-ray crystallography in 1912. At the time, all the calculations were done by hand – they won a Nobel Prize in 1915 for their work. The method has been used to solve the structures of many important molecules. In the 1950s Francis Crick and James Watson used pictures of DNA taken by Rosalind Franklin to solve the DNA structure. Dorothy Hodgkin determined the structures of the antibiotic penicillin (1946), vitamin B12 (1956) and insulin (1969), winning a Nobel Prize in 1964.

Key Principles and Instrument

When the X-ray beam hits the crystal, a pattern of spots is made on the screen at the other side. Complicated mathematics called Fourier transformation (FT) is applied using a computer to change the spot pattern into a picture showing how the particles in the crystal are arranged. In the instrument, the sample is mounted on to a goniometer, which is used to position the crystal into specific orientations so that it can be analyzed from multiple angles. X-rays are generated from an X-ray tube, and they are then filtered so that they are monochromatic, i.e. of a single wavelength frequency. The atoms in the crystal refract the X-rays and the X-rays are elastically scattered on to a detector, they have the same energy as the incident X-rays that are fired at the

sample. This generates a 2D diffraction pattern of the crystal in a single orientation.

Applications of X-Ray Crystallography in Pharmaceuticals

Solid State Characterization:

Powder X-Ray Diffraction (PXRD)

Powder X-ray diffraction (PXRD) measures the diffraction pattern of crystalline material in powder form as opposed to single crystal. PXRD is one of the most common bulk techniques used for the analysis of powders and is similar in concept to the single-crystal analysis, except the data is generated on the bulk powder instead of a single crystal. Each API produces a specific pattern depending on the structure of its crystal lattice. Each polymorph, salt, or co-crystalline material will exhibit its own specific pattern. For this reason, PXRD of the API can be done in controlled environmental conditions, using hot stage and/or controlled humidity environments in order to study the chance of any form conversions (e.g., hydration/dehydration). In addition to this, it can be used to determine if any change in crystalline form (e.g., hydration, salt disproportionation) in the drug product has occurred during the APS study. This relies on the presence of detectable diffraction peaks of both the ingoing API form and the forms to which it may convert at the formulated levels. In addition, the API peaks must be distinguishable from any crystalline excipient peaks. PXRD is also used for qualitative as well as quantitative determination of the degree of crystallinity of the pure API. Disorder leads to peak broadening in the powder pattern, and eventually an amorphous 'halo', a broad peak is obtained (see Fig-4).

Polymorphism and its Significance in Pharmaceutical Industry

Most drug molecules are highly functionalized and can self-organize in several ways in the solid state with nearly the same lattice energies. Due to this property, many drug substances crystallize in different arrangement of the molecules in the crystal. This ability of the substances to crystallize in different crystalline forms is called polymorphism. Screening for various solid forms of an API and selection of the right form is a critical step in drug development.

APIs may exist in multiple crystalline forms such as salts, hydrates, solvates,

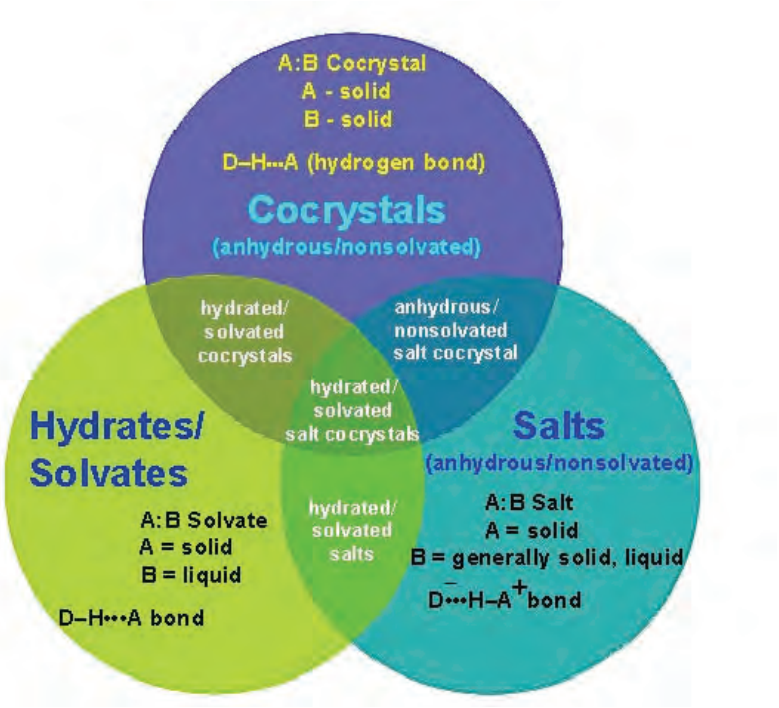


Fig-1: Inherent Overlap of Multi Component Solid Forms

co-crystals and their polymorphs (See Fig-1). These distinct solid forms impact physico- chemical properties of the API and offer solutions to solubility, stability, bioavailability, and patenting issues in drugs. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product.

There are a number of methods that can be used to characterize polymorphs of a drug substance. Demonstration of a nonequivalent structure by Single Crystal X-Ray Diffraction is currently regarded as the most definitive evidence of polymorphism. X-ray powder diffraction (PXRD) can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic resonance [ssNMR]) are helpful to further characterize polymorphic forms.

In fact XRD in combination with above mentioned techniques has revolutionized the solid state characterizations and brought useful innovations in the form of novel polymorphs, solvates, co-crystals and stabilized pharmaceuticals.

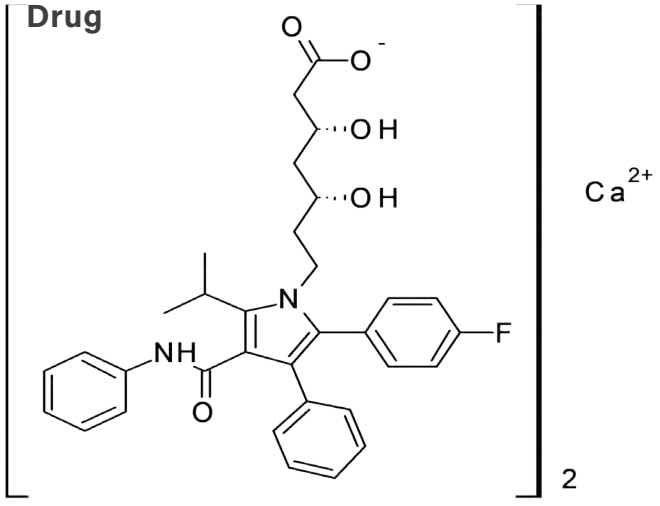
Solvates: Emerging Tool in API Development

Solvates are multi component crystal forms generally containing stoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate. Pharmaceutical chemists face many challenges in the lab and manufacturing due to issues related to scalability of various forms of a given solid form, and solid form inconsistencies.

Due to difference in their physical

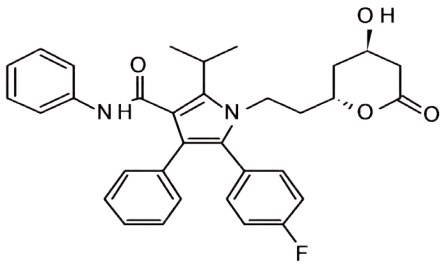
properties such as polarity and solubility, solvates sometimes also serve as tools in the purification of API. Recently, solvates of several drug molecules have been isolated with an aim to purify them, otherwise difficult to purify by conventional techniques. In

Drug



Atorvastatin Calcium

Intermediate



Atorvastatin lactone

atorvastatin, difficulty in the isolation of lactone is one of the reasons that Ca salt of the open dihydroxy acid is recommended as drug. The lactone form has not been described in the prior art with respect to the existence of polymorphism. We developed a process for the preparation of novel crystalline solvates such as DMSO solvate of atorvastatin lactone (DMSO content 17-22%, m pt 127-130 as supported by TGA). DMSO solvate (see Fig-2) was used for the isolation of lactone in highly pure form, leading to an efficient process technology for the removal of unwanted impurities from the API.

Solvates of anti-cancer drugs Sorafenib and lenalidomide have been well established and used as purification tools for API. There are many drug molecules in which solvate formation is a common occurrence, therefore, some are recommended in the form of solvates. For example darunavir ethanolate and estradiol which forms solvates with 30 solvents. Desolvation leads to the formation of other form, atorvastatin lactone DMSO solvate leads to the formation of amorphous form after desolvation as confirmed by its PXRD (see Fig-4). As per the new US FDA guidance on Chemistry, manufacturing, and controls (CMC) information regarding polymorphic integrity of drug substance must be submitted to support the approval of an abbreviated new drug application (ANDA).

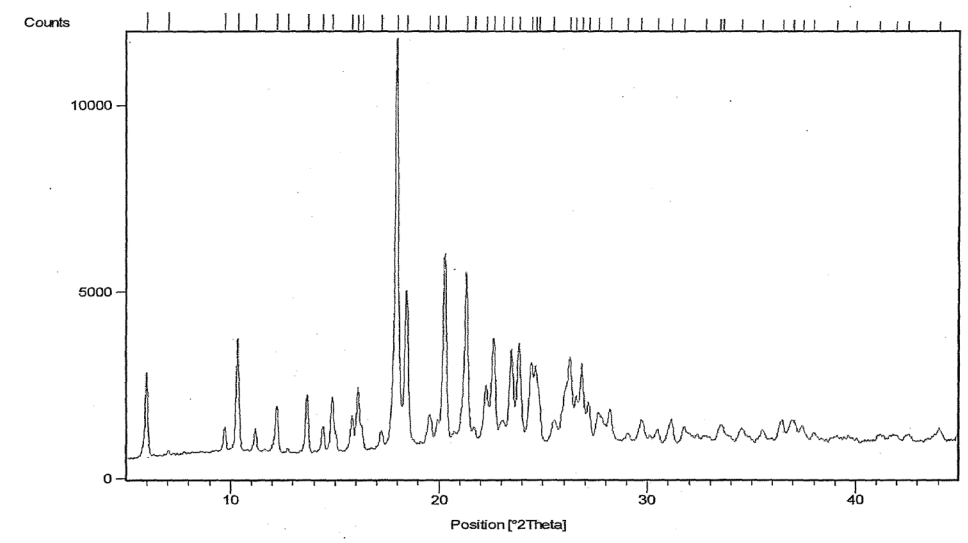


Fig-2: PXRD-Crystalline Atorvastatin Lactone DMSO Solvate

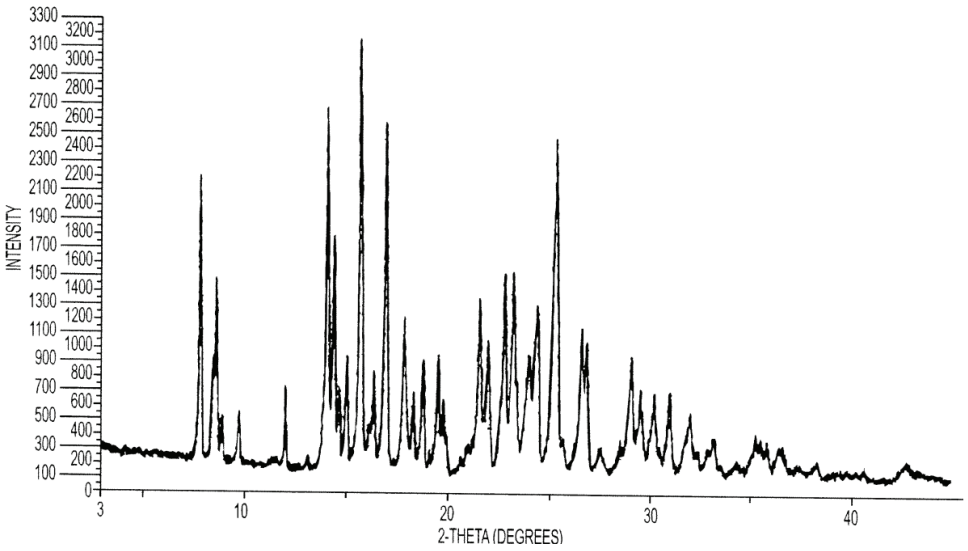


Fig-3: PXRD of DMF Solvate of Anticancer Drug Lenalidomide
DSC shows endotherm at 263 deg TGA: weight loss 13% at 146 deg C

Polymorphism and Patents: From Innovator and Generic Perspective

Polymorphism is playing an increasingly important role in establishing and protecting intellectual property rights in the pharmaceutical industry. As in the analysis and characterization of polymorphs a variety of analytical methods may be used in patent specifications. The preparation, prosecution and protection of a patent involving polymorphs is a challenging scientific and legal activity.

Generic's Perspective: Reverse Engineering is being extensively used by generic pharma companies for the determination of Polymorphic Forms of API in Innovator Tablets. Powder XRD (PXRD) is the handy main identification tool for the polymorph determination in innovator tablets because of non-availability of pure API used by the innovator and absence of samples of pure polymorphs. Discovery and development of alternate or novel polymorphs other than innovator's morph of a patented drug by a generic

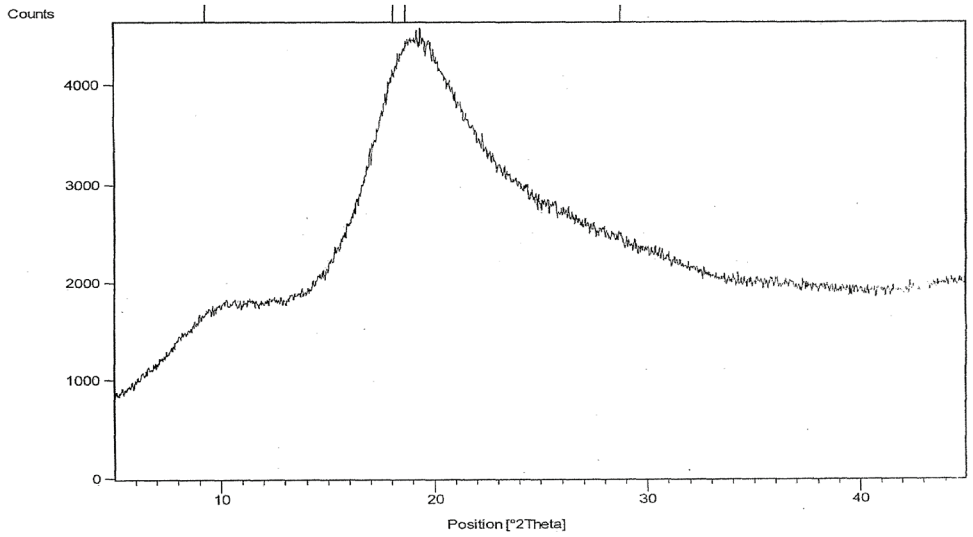


Fig-4: XRD of Atorvastatin Lactone Amorphous

company provides an opportunity for paragraph IV certification: the first ANDA approved with P-IV certification is entitled for 180 days marketing exclusivity. Novel or alternate polymorphs are also developed to block other generic launches with the help of marketing exclusivity and patent protection for some time.

Innovator's Perspective: Innovator companies extensively study the polymorphism of new drug molecules to identify the most suitable form with respect to solubility and stability as early as possible. Other objective of this study is to delay generic entry by filing patents, covering solid forms in the Orange book. By this innovator gets the advantage of 30 months stay in case of generic ANDA's para IV certification. This strategy is called IP Fencing.

Latter enhances the product life cycle by blocking generic entry by building a product portfolio around different forms- also called "ever greening of patents".

Drug Design: Investigating protein function and interaction, as well as developing direct drug design strategies requires structural information provided by X-ray crystallography. The Nobel Prize in Chemistry 2009 was awarded to V. Ramakrishnana, T. Steitz and A. Yonath for their work in the field of structural and functional studies of ribosomes wherein they applied X-ray crystallography most often during these studies.

Protein Structure: The elucidation of a macromolecular structure at the atomic level by X-ray or neutron diffraction analysis requires the compound to be formed into relatively large single crystals without any inclusions. Though protein crystallization is very difficult because of the fragile nature of protein crystals, many soluble proteins, membrane proteins, nucleic acids, and

nucleoprotein complexes have been obtained in a crystalline form suitable for crystallographic investigation. When a solution of a biopolymer is brought to supersaturation, the biopolymer may form crystals suitable for X-ray diffraction analysis, an amorphous precipitate, or any physical form between these two extremes. Parameters such as pH, temperature, chemical composition of the crystallization solution, and the rate of supersaturation determine whether an amorphous precipitate or crystals are formed. Supersaturation is often achieved by increasing the concentration of precipitating agents in the crystallization solution. Auxiliary substances may improve crystallization or may initiate crystallization in otherwise static solutions.

Conclusion

X-Ray Crystallography has emerged as a powerful tool in the last few decades for the accurate determination of molecular structure at atomic resolution. Principles of Powder X-Ray Diffraction in combination with DSC, TGA, Raman, etc. have revolutionized the solid state characterization of pharmaceuticals. Single crystal X-ray diffraction and PXRD are currently regarded as most definitive evidence of polymorphism and are used to determine the polymorphic integrity of drug substances as per US FDA guidance. Innovator and Generic companies must continue to evolve this area to innovate novel Polymorphs, Co-crystals, Solvates and Stabilized Products to meet the medical needs. ■

About Author:

Dr Rajesh Kumar Thaper has held several senior R&D positions in top pharmaceutical organizations like Ranbaxy, Lupin, Dr Reddy's and Jubilant. He has over 27 years of rich experience in Technology, Innovation and Execution. He has about 120 Patents and several scientific Publications to his credit and developed over 100 molecules.

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Hydroxychloroquine Controversy for its use in COVID-19: A Drug Metabolism and Pharmacokinetic Perspective and Guidance to Physicians

There has been intense interest in Hydroxychloroquine (HCQ) since it is being prescribed off-label for many SARS-CoV-2 infected patients. Despite, several clinical studies with mixed results, many physicians prescribe HCQ claiming that it reduces the incidence of mortality due to COVID-19 disease, when given early enough. Randomized clinical trials, however, indicate that this drug may be marginally effective for COVID-19 patients. Many COVID-19 patients take several other medications for pre-existing co-morbidities, thus HCQ's cardio toxic potential with QTc prolongation has emerged as the major concern. Regulatory agencies such as the US-FDA felt that risk to benefit ratio is very high for HCQ in treatment of COVID-19 patients and thus revoked its Emergency Use Authorization (EUA) and placed a warning for its unauthorized off-label use. Nevertheless, the controversy still continues as many physicians wrote to US-FDA to approve its use to treat COVID-19 patients. There are reports that many frontline workers, including many physicians, are consuming HCQ assuming it can be prophylactic to prevent SARS-Co-V-2 infections. In addition, many in the general public may be consuming high doses of herbal concoction along with HCQ.

In the past three decades it has been recognized that, undesired Drug Metabolism, Transport and Pharmacokinetic (DMTPK) has become the primary reason for many fatal drug-drug interactions (DDI). Several drugs have been withdrawn from the market or issued black-box warnings due to fatal DDI or drug-herbal interaction (DHI). Therefore, in this commentary, we reviewed the available literature on DMTPK for HCQ and how other drugs may influence HCQ metabolism and transport and, as a consequence, how other drugs modulate PK properties of HCQ or vice versa HCQ modulates PK properties of other drugs. Based on our literature review, we recommend that physicians treating COVID-19 patients must take into account DMTPK properties of HCQ and temper its dose to prevent fatal overdose and DDI /DHI

BACKGROUND:

Hydroxychloroquine (HCQ; brand name: PLAQUENIL, sold as HCQ-sulfate), was first approved in 1955 by US-FDA, as anti-malarial drug. Since then due to its immune-modulatory and anti-inflammatory properties it has been repurposed for Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA). Recommended dosages and dose frequencies are listed in Table 1.

Hydroxychloroquine warnings:

- Accidental swallowing by children.
- Do not use or tell your doctor if any persistent skin problems (e.g., psoriasis, skin rashes).
- High doses can cause permanent vision problems. An entire book is devoted on HCQ and Chloroquine induced retinopathy - to guide physicians who prescribe these medications for patients of malaria, SLE and RA.
- May cause fatal heart disease with heart rhythm problems. Combination with other drugs can potentiate these heart arrhythmias.
- Severe hypoglycemia induced by HCQ and therefore, dose reduction of Insulin and anti-diabetic medications is required.
- Mental health effects including mood swings and suicidal tendencies.
- Skin allergies (hives, swelling) – Appears to be an immunologic

Malaria Prophylaxis	Uncomplicated Malaria	Lupus Erythematosus	Rheumatoid Arthritis
310 mg once weekly	**620 mg followed with 310 mg at 6 hrs, 24 hrs, and 48 hrs (Total 1550 mg)**	**155 mg to 310 mg. Once daily as a single dose or two divided doses. Doses above 310 mg are not recommended**	**310 mg to 465 mg as a single daily dose or in two divided daily doses. After good response obtained the doses can be reduced to 155 mg to 310 mg). Do not exceed 465 mg daily dose or (5 mg/kg as a base)**

Table 1: Approved treatment regimens of Hydroxychloroquine for Malaria, Lupus and Rheumatoid arthritis

reaction.

- Unusual bleeding due to rupture of erythrocytes for people with glucose-6-phosphate dehydrogenase deficiency. Blood clots are also noted as major toxic event by SAS-CoV-2 infected patients. Thus, HCQ may potentiate SARS-CoV-2 bleeding in a synergistic manner.

The most serious adverse event of HCQ is cardio toxicity involving QTc prolongation and induced arrhythmia potentially leading to death. This can be due to accumulation of HCQ or its major metabolite Desethyl-HCQ (DHCQ). At least three potential mechanisms explain this accumulation of HCQ and DHCQ. (1) Over dosing. (2) DDI or HDI, (3) Cytokine storm induced down-regulation of CYP enzymes and HCQ metabolism. As such random and unsubstantiated use of HCQ in COVID-19 patients is of extreme concern.

PHARMACOKINETICS OF HCQ:

Bioavailability (%)	74 ± 13
Half-life	30 – 52 days
Peak plasma (T_{max}) HCQ concentration time (h)	2 - 4
C_{max} – Blood & Plasma (200 mg oral dose)	129.6 ng/mL & 50.3 ng/mL
Plasma concentration range males (400 mg dose)	222-1913 (ng/mL) (median 746)
Plasma concentration range females (400 mg dose)	208-3316 (ng/mL) (median 932)
Plasma concentrations 400 mg QD	949 ng/ml (range 208–3,316 ng/ml)
Plasma concentrations 200 mg BID	867 ng/ml (213–2,452 ng/ml)
Median blood HCQ concentration (ng/mL) –Caucasians	931
Median blood HCQ concentration (ng/mL) –African Americans	901
Median blood HCQ concentration (ng/mL) – North Africans	843
Median blood HCQ concentration (ng/mL) –Asians	1037
Volume of distribution (Vd) – Blood & Plasma	5522 L and 44, 527 L
Clearance	96 mL/min
Time to achieve seady-state in blood and plasma concentrations	6 months
Protein Binding	29 – 64 %
Hepatic Metabolism	CYPs – Primary CYP3A4, Secondary CYP2D6 , CYP2C8
Desethylchloroquine	18 %
Desethylhydroxychloroquine	16 %
Drug transport	SLCO1A2, and SLCO1B1
Excretion	40 – 60 % (unchanged drug; Kidney and Liver)
Tissue distribution (rat)	Spleen>Lung>Liver>Kidney>Eye>Muscle

Table 2: Known pharmacokinetic characteristics of hydroxychloroquine in humans

CYP Enzyme	% Total (approximate)	Extent of Variability (approximate)	% Drugs Metabolized
1A2	13	40-fold	2
2A6	4	30-100 fold	2
2B6	<1	50-fold	---
2C	18	25-100	10
2D6	Upto 2.5	1000-fold	30
2E1	Upto 7	20-fold	4
3A4	Up to 60	90-fold	50

Table 3: Human hepatic Cytochrome P450s their variability and contribution to drug metabolism

Pharmacokinetics (PK) of HCQ in human populations has been well established (Table 2 with estimated bioavailability > 60%. Following a single 200 mg oral dose, HCQ reached a mean Cmax of 129.6 ng/mL with a mean Tmax of 3.26 h in the blood and a Cmax of 50.3 ng/mL with a Tmax of 3.74 h in the plasma. The mean levels of HCQ in whole blood were approximately two-fold higher than in plasma, suggesting that HCQ is widely distributed into extra vascular tissues including red blood cells (RBC). This behavior is consistent where estimate volume of distribution (Vd) of HCQ was 5522 L and 44,257 L in blood and plasma, respectively. Tissue distribution studies in rats showed that HCQ accumulates in Spleen>Lung>Liver>Kidney>Eye>Muscle and the accumulation is dose-dependent. Approximately, 40-60% of HCQ is excreted by the kidneys, 8-25% is excreted via feces, 5% distributed to skin, and 25-45% is stored in lean tissues.

HCQ absorption via gut may be completed in 3-12 h but its clearance from the body takes several days. A single 200 mg oral dose of HCQ has an elimination half-life (T1/2) of 537 h (22.4 d) in blood, and 2963 h (123 d) in plasma. A 155 mg intravenous dose has T1/2 of 40 days. The estimated Clearance (CL) of HCQ is 96 mL/min. A period of 6 months is required to achieve 96% of steady-state levels of HCQ with the usual once daily, oral dosage regimen.

HCQ is a racemic mixture, with the S-enantiomer is 64% protein bound in

FUNCTION	ALLELE	AFRICAN AMERRICAN	CAUCASIAN	INDIAN (INDIA)	ASIAN	HISPANIC
NO FUNCTION	*4	4.0	18.7	16.1	5.2	12.7
DECREASED FUNCTION	*17	16.8	0.3	2.7	0.2	1.9
	*29	9.4	0.1	1.4	0	1.6
	*35-*10	0.2	0.1	0.2	10.4	0.2
	*41	2.5	9.6	8.2	4.4	5.7
NORMAL FUNCTION	*1	33.2	37.3	37.5	33.5	45.9
	*2	11.6	0.3	1.9	0.2	1.3
	*2A	5.1	15.6	14.4	11.0	17.1

Table 4: Intra-ethnic and inter-ethnic variations in CY2D6 genetic polymorphisms

plasma where as its R enantiomer is 37% protein bound in plasma. Within plasma compartment, S-HCQ is 50% bound to serum albumin and 29% bound to alpha-acid glycoprotein. The R-HCQ is 29% bound to serum albumin and 41% bound to alpha-acid glycoprotein.

Huge variability (> 10-fold) of blood and plasma concentrations was observed when HCQ was administered to Lupus patients. In 171 patients with Lupus Nephritis, HCQ Levels while taking 200 mg/day were lower than while taking 400 mg/day (0.58 ± 0.47 versus 0.79 ± 0.54 mg/L). Factors affecting HCQ levels were analysed and found HCQ concentrations in obese patients were significantly lower than non-obese patients. However, with the limited literature, no statistical difference in PK of HCQ was observed in relation to age, gender or ethnicity (CYP2D6 polymorphisms). Nevertheless, due to high intra- and inter-subject variability of HCQ, the factors those affect PK could be due to multiple reasons and not limited to one single factor. These may include:

A) Multiple CYP enzymes catalysing the metabolism of HCQ with Intra- and Inter-individual variability in expression.

B) Intra-ethnic and inter-ethnic genetic polymorphisms.

C) Diet and Environment modulating the up- and down-regulation of CYP enzymes and drug transporters.

D) Down-regulation of CYP and transporters by Cytokine storm during infections and inflammation.

E) Competitive inhibition of CYP enzymes and transporters by other drugs inhibiting HCQ metabolism or vice versa.

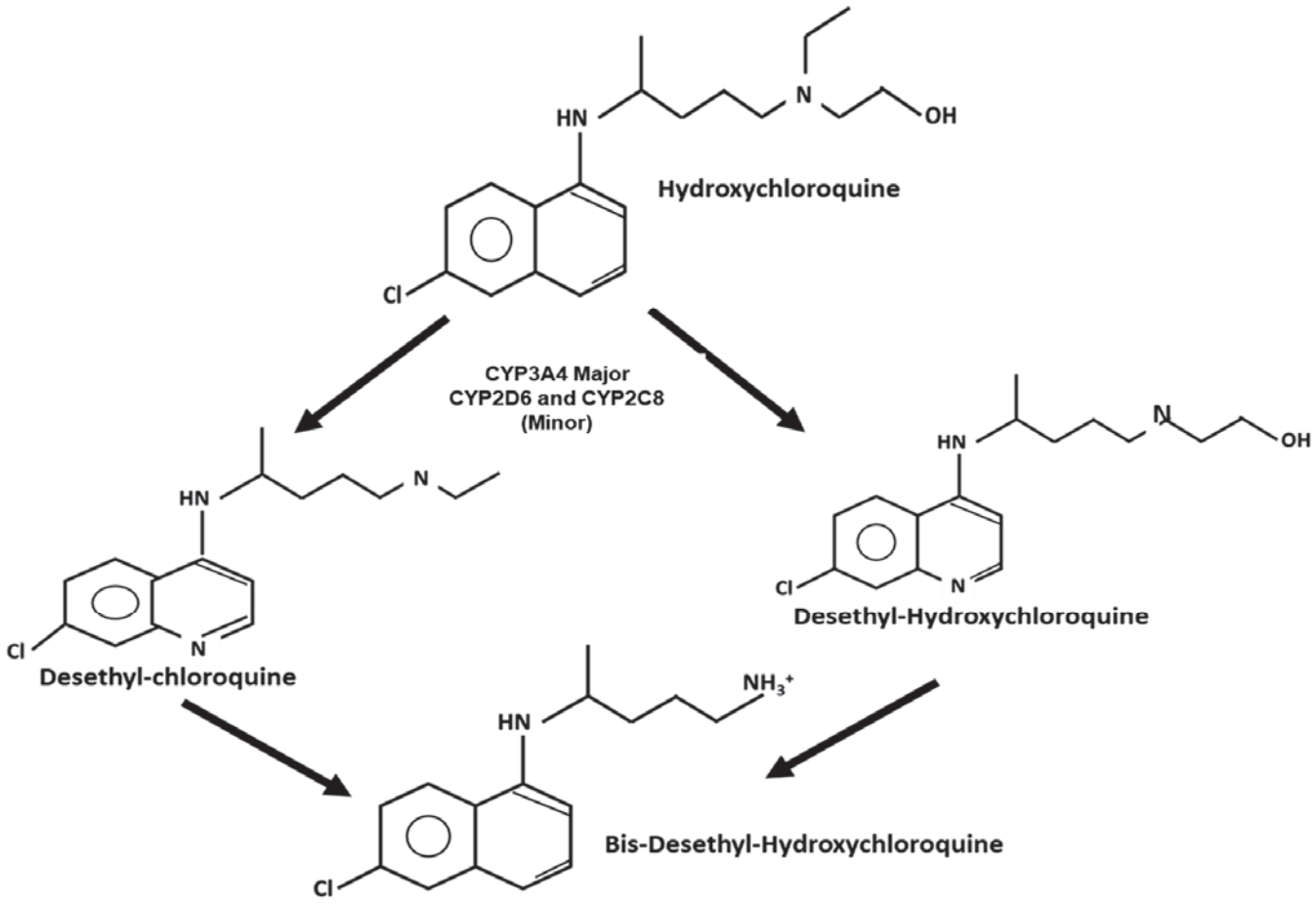

Figure1: Hepatic metabolism of Hydroxychloroquine by Cytochrome P450 enzymes

METABOLISM OF HYDROXYCHLOROQUINONE BY HEPATIC CYTOCHROME P450 ENZYMES:

CYP3A4 and CYP2D6 catalyze the metabolism of nearly 80% or more of the drugs currently present in the market (Table 3). While CYP3A4 catalyzes at least 50% of the known drugs, CYP2D6 contributes to 30% of drugs on the market. Table 3 also shows the variability of CYP enzyme expression in human populations, while CYP3A4 variability is 90-fold and CYP2D6 variability is 1000-fold, in humans.

CYP enzymes can be inhibited by other drugs or herbs, leading to DDI or DHI. CYP enzymes and transporters can also be transcriptionally activated by many drugs and dietary agents through nuclear receptors (e.g. Pregnane X receptor for CYP3A4 induction), resulting increased enzyme levels. In addition, cytokines during inflammation and infections, can down-regulate these enzymes (Figure 2).

All these factors contribute to extensive variability in DMTPK of HCQ and it is, therefore, not surprising that HCQ plasma concentrations have very high

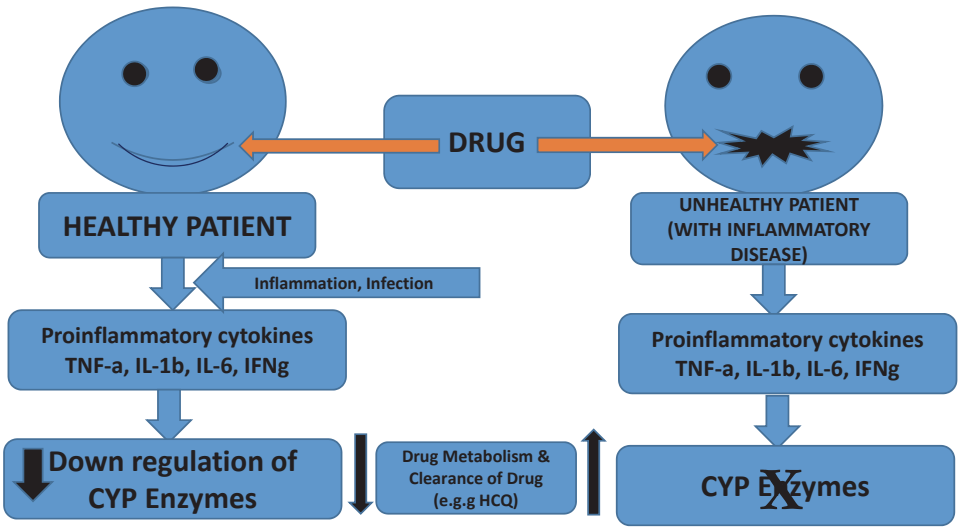

Figure 2:Effect of Cytokines on Cytochromes P450 Enzymes and Drug Disposition

variability in humans. In addition, extensive literature testifies the DDI potential of HCQ (Table 5) and patients taking other drugs for comorbidities may result in fatal cardiotoxicity (QTc prolongation). Table 6 shows some drugs withdrawn from market due to fatal DDI. For an exhaustive list of more than 1000 compounds, those interact pharmacokinetically or pharmacodynamically, with HCQ, the reader can consult the web page,

https://go.drugbank.com/drugs/DB01611.

During pharmaceutical drug development, PK and toxicokinetics (TK) play an important role in drug dosage selection and frequency of its administration in patients. The ideal elimination half-life of a drug is approximately 8 – 12 hrs in blood plasma. Anything beyond that is carefully evaluated for multiple daily dosing frequency. For example, a drug like HCQ with half-life 0f 50 days, cannot be administered daily as it can accumulate beyond threshold concentrations for toxicity. In fact, low blood concentrations of HCQ has been a better predictor of efficacy of SLE, rather than dose of HCQ. Regulatory agencies including FDA give high importance for PK half-life, metabolic clearance and associated variability in humans. In addition, HCQ alters PK of several co-administered drugs (due to competition for metabolism by same CYP enzyme or transporter) and the list of drugs in Table 4 shows that at least 30% of marketed drugs can increase QTc prolongation when co-administered with HCQ. Similarly, co-administration of high doses of herbal concoctions should be avoided as many of the chemicals in these concoctions can also inhibit CYP enzymes and drug transporters.

Cytokine storms, a characteristic feature of SARS-CoV-2 infection, can potentially down-regulate CYP enzyme and transporter expression (Figure 2). This can have serious impact on HCQ metabolism during SARS-CoV-2 infections. HCQ concentrations may increase beyond

Drug	Effected Organ	Mechanism of Toxic action
Drugs those cause cardiac arrhythmias Heart		
Digoxin	Heart	Metabolic Interactions - Risk or severity of QTc prolongation can be increased when HCQ is combined with any one of these drugs.
Azithromycin (antibiotic)		
Ciprofloxacin (antibiotic)		
Chlorpromazine		
Verdanafil		
Losartan		
Drugs those effect blood sugar levels		
Insulin	Blood sugar	Co administration of HCQ can increase efficacy (increased hypoglycemia) of anti-diabetic drugs
Metformin		
Chlorpromamide		
Glipizide		
Glimepiride		
Glyburide		
Anti-seizure Drugs		
Phenytoin	CNS	Co Administration of HCQ with these drugs may result in less effectiveness of these drugs against seizures
Carbamazepine		
Immunosuppressants		
Cyclosporin	Increased immunosuppression	Co Administration of HCQ with Cyclosporin may increase blood levels of cyclosporine
Dexamethasone		Risk or severity of adverse effects can be increased when Dexamethasone is combined with Hydroxychloroquine
Vaccines		
Adenovirus Type 7 vaccine live		Risk or severity of infection can be increased when Adenovirus type 7 vaccine live is combined with HCQ
Anthrax vaccine		Risk or severity of infection can be increased when Anthrax vaccine is combined with HCQ
Antiviral drugs		
Lopinavir	Viral replication inhibition	Serum concentrations of anti-viral drugs can increase when combined with HCQ. Therapeutic efficacy of remdesvir may decrease with HCQ
Ritonavir		
Remdesvir		

Table 5: Known Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions of Hydroxychloroquine

threshold levels and perhaps responsible for observed QTc prolongations in many patients.

Controversy on HCQ as an antiviral drug: Relevance of in vitro cell culture data to humans:

Besides variability in pharmacokinetics of HCQ, the efficacy of HCQ against SARS-CoV-2 is also debated considerably. In early 2000s during SARS-CoV-1 outbreak, some researchers found that entry of SARS-CoV-1 into VERO-E6 cell line (derived from kidneys of AFRICAN GREEN MONKEYS) was inhibited by HCQ. These authors concluded that HCQ can act as an anti-viral agent. Recent studies, using SARS-CoV-2 confirmed those results showing HCQ inhibits the viral entry in VERO-E6 cells. However, when HUMAN DERIVED Calu-3 cell line was used, HCQ was unable to block the entry of SARS-CoV-2 into these cells. Mechanistic studies showed that viral entry into VERO-E6 cells is aided by a helper enzyme, Cathepsin L, after virus binding to ACE 2 receptor. HCQ inhibits Cathepsin L and therefore prevents

its entry into VERA-6 kidney cells. Interestingly, in hCALU-3 cells another helper enzyme TMPRSS2 aids the viral entry into cells after virus binding to ACE 2 receptors. The data confirms that HCQ does not inhibit TMPRSS2 and therefore it does not prevent viral entry into human cells. Therefore, the in vitro data should be carefully reviewed before making huge, leaping interpretations. Several clinical trials with HCQ were conducted on the basis of VERO-E6 monkey kidney cell data but these data only support potential utility of HCQ as an antiviral drug for monkeys, but not in humans.

RECOMMENDATION FOR PHYSICIANS:

The doctors are the primary conduit for drug treatment of patients. Pharmaceutical researchers, conduct 7 – 10 years of regulatory mandated research to release one drug into market, they cannot treat patients. Therefore, doctors and pharmaceutical scientists should communicate effectively in order to understand the pharmacology, PK, drug metabolism (and other ADME properties), regulatory toxicology on how a dose and frequency of dosing is selected for human treatment. Unfortunately, for HCQ such data was not generated when it was originally released into market in 1950s. However, beginning late 1980s PK and TK have become integral part of drug discovery and development process before initiating human trials. Since then understanding of PK, variability, cardio toxic potential with DDI have become known for HCQ. However, such data should be part of Continuing Medical Education for doctors to ensure safety for patients.

With regard to HCQ treatment, not only for COVID patients, but also for RA, Lupus and Malaria patients, doctors should ensure frequent ECG monitoring along with drug concentration measurement in blood plasma to ensure no untoward harmful effects of HCQ in patients. Highly sensitive LC-MS/MS techniques for analysing HCQ and its metabolites in human body fluids are available now and doctors should work with pharmaceutical CROs to source these analytical tools. In addition, doctors should also conduct pharmacogenetic SNP analysis on patients' blood samples to identify them as poor metabolizers, extensive metabolizers and ultra-rapid metabolizers – so that they can adjust the dose of the treatment drug accordingly.

CONCLUSION: HCQ should not be used to treat COVID-19 patients as it is not effective as an antiviral drug as well as it can cause potential cardio toxic interactions with other co administered drugs for comorbidities. When it is used, extreme caution should be taken to temper its use either as monotherapy

Drug	Mechanism of toxicity
Astemizole	Fatal arrhythmias
Grepefloxacin	Cardiac repolarization and QT prolongation
Sparfloxain	QT prolongation and phototoxicity
Sertindole	Arrythmias and sudden cardiac arrest
Terfenadine	QT prolongation and Ventricular tachycardia
Terodiline	QT prolongation, ventricular tachycardia and arrhythmias
Thiorizadine	Severe cardiac arrhythmias
Chlorphenteramine	Cardiovascular toxicity
Cisapride	Fatal cardiac arrhythmias
Clobutinol	Ventricular arrhythmias and QT prolongation
Cloforex	Cardiovascular toxicity
Dexfenfluramine	Cardiotoxic
Dimethylamylamine	Cardiovascular toxicity
Dogetilide	Drug interactions, QT prolongation
Encainamide	Ventricular arrhythmias
Posicor	Serious fatal drug-interactions

Table 6: Some Drugs withdrawn from the market due to Cardiac toxicities
please cons For an exhaustive list ult, https://en.wikipedia.org/wiki/List_of_withdrawn_drugs

or more specifically as polytherapy with drugs that could impact its DMTPK along with frequent ECG monitoring in humans to circumvent serious adverse events. Regular HCQ assaying and individual tailoring of treatment might help to improve the safety and efficacy of HCQ treatment in COVID-19/SLE/RA/ malaria patients. Prophylactic use of HCQ by frontline workers should be stopped immediately. ■

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Note added in proof (https://www.springer.com/gp/book/9781493905966) :

Malpractice settlements are large for undetected hydroxychloroquine and chloroquine toxicity which, if untreated, can lead to permanent loss of central vision. Knowledge of the ocular toxicity of these drugs has increased during the past fifty years as their use has expanded. HCQ and Chloroquine Retinopathy is the first single-source book on the subject and is essential for the practicing ophthalmologists, rheumatologists, dermatologists, and internists who prescribe these drugs. It covers clinical topics such as signs and symptoms of toxicity, toxicity screening, ancillary testing, to whom and why the drugs are prescribed and dosing considerations. Additionally, the book addresses practice management considerations, including coding, reimbursement and equipment costs, and the medico-legal responsibilities of the rheumatologist and of the ophthalmologist. Guidelines for the management of hydroxychloroquine and chloroquine vary around the world and differences between the guidelines of the United Kingdom, the United States, and other countries are identified. The book concludes with a collection of case examples illustrating common clinical scenarios and their management. This book is a "must-have" resource for physicians who use these drugs.

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Navigating the regulations for Life Sciences and Healthcare in the new normal

The pandemic has drastically impacted global working models across the industries. Individuals in altered industries have learnt to work in varied shifts by successfully adapting work from home models & delivering outputs as per client obligations & regulatory compliance. Certain occupations, although previously characterized by high human proximity and low suitability to work from home, may well be amenable to this shift through innovation and technology-enabled business models. This new model has influenced and encouraged usage of modern tools & technology, automation, big data & analytics, social media surveillance on global aspects.

Around the world, overall management and planning of the Lifesciences and Healthcare industry has also been impacted, along with global clinical trials. Regulators have made changes in their strategies too. The Medical Device sector is continually contributing and collaborating with policymakers and other stakeholders to play its part in ensuring that people's lives and health can be protected with uninterrupted supply. As per World Health Organization "Governments should develop incentives for industry to ramp up production. This includes easing restrictions on the export and distribution of personal protective equipment and other medical supplies."

On 25 March 2020, the EU Commission decided to postpone the implementation of Medical Device Regulations (EU) 2017/745 (MDR) by a year to 26 May 2021. This allows the medical device industry and Notified Bodies (NBs) to focus on the problem at hand and put all their efforts into combating the current situation.

On March 25, 2020 in the interest of the protection of health, UK Medicines and Health Regulatory Authority (MHRA) announced that it may authorize the supply of non- Conformitè Europëenne (CE)-marked devices. US Food and Drug Administration (FDA) opened the door for Emergency Use Authorization. Some of the counties called on the automotive, aerospace and other industries to help

plug the shortages of important medical devices. Mechanical Ventilators also created an open-source solution for Ventilators and regulators emphasized on the safety and performance of the devices. However, this may have created training and understanding gaps for Healthcare professionals. Here, companies have the opportunity to set up a Medical information Contact Center, to respond to inquiries related to Medical Information and Product support.

Global Regulatory bodies have also assessed the impact of the pandemic and issued new guidance for management of clinical trial and Post marketing surveillance. Key health authorities, including the US FDA, European Medicines Agency (EMA) and the MHRA have released guidance for stakeholders. Few are below,

- MHRA guidelines conveys that every effort should be made to prioritize timely submission of suspected unexpected serious adverse reactions (SUSARs). Sponsors should remain compliant with safety reporting and investigators should continue to collect adverse events from study subjects.
- The French Agency (ANSM) guidance has provided flexibility in safety reporting compliance. SUSARs should still be submitted based on existing requirements, however, a two-month delay is allowed for submission of Development Safety Update Reports (DSURs). FDA guidance on conducting clinical trials during COVID-19 recommends that sponsors should weigh safety assessment methods ensuring the safety of trail subjects & avoid unnecessary contact.

With the new guidance in place, Market Authorization Holders (MAHs) & service providers should be cautious, careful and proactive in defining the pandemic effects, to minimize the impact on clinical trials & maintains patient safety.

With new regulatory changes, and the global pandemic, the Lifesciences and Healthcare industry is predicted to increase focus on Clinical trials, Pharmacovigilance & Medical devices outsourcing services in the coming years. This growth is attributed to rising number of health issues majorly in the paediatric and elderly population. This has led to implementation of advanced healthcare facilities, efficient and effective treatment & humongous medical plans proposed by national government bodies to provide better care to the patients. Pharma companies are assessing and validating tools, automated solutions & social media surveillance to provide scientific patient centric safety approach, diseases awareness, treatment regimen, real time tracking & monitoring for clinical trials & adverse events to meet regulatory compliance.

The pandemic has created extraordinary circumstances that require substantial additional resources and an increased availability of vitally important medical devices. The FDA suggested that companies should develop and implement a continuity of operations plan to follow during such situations, that involves investment in reporting and accountability. Healthcare professionals understand the value of reporting, however, there are still Challenges for Adverse Event and/or Incident report. Few of them are failure to recognize the Event or Incident, lack of time, complex documentation, lengthy reporting procedures, patient confidentiality concerns, fear of blame, employee absenteeism. Prompt reporting is pragmatic and arguably, the best method for safety surveillance. Under reporting or the delay in reporting can be catastrophic. Besides Devices, new medicines that will be launched and related risks has an impact on the manufacturing units to meet regulatory compliance. However, this creates opportunities for new business revenue.

The growing rate of the elderly population is adding significant increase in Pharmacovigilance Outsourcing Market too. According to WHO, the world's elderly population, older than >60 year, is estimated to reach 2 Billion by 2050 from 800 million in 2014. These statistics drives significant demand for old age medical care and nursing support along with provision of homecare facilities that is further estimated to drive notable opportunities in the global Pharmacovigilance Outsourcing Market over the forecast period i.e. 2019-2028. This generation is highly prone to serious health conditions such as heart problems, diabetes, cancer, paralysis, arthritis, rheumatoid arthritis, seizures, glaucoma, cataracts etc. that requires continuing assessment of adverse events developed from usage medicines along with ensuring product risk safety & medical treatment. To perform better tracking and monitoring of adverse events across global patients, the implementation of automation, tools and technologies are needed for faster assistance to human kind in managing their healthcare conditions.

Healthy partnership with a Long-Term value-driven approach to Pharmacovigilance

The current pharmacovigilance and clinical trials services have been disrupted due to enforced lockdowns and businesses are pushed to adapt a new working model with virtual support by implementation of tools, technology and automation. To analyze the data received from various sources, sponsors are highly depended on synergy between traditional analytics and validated clinical data for providing faster and better treatment to worldwide

patients ensuring safe drug usage. Travel restrictions imposed by the pandemic has also resulted in the due diligence activities.

The pandemic has brought lot of challenges and opportunities for global pharma and life science industry for Data complexities, regulatory compliance and stringent timelines. Pharmacovigilance market surveys and implementation of automation and tools will help global clients in timely reviews on their product risks and safety and meet compliance, understand risks during early phase of drug development, and be able to serve

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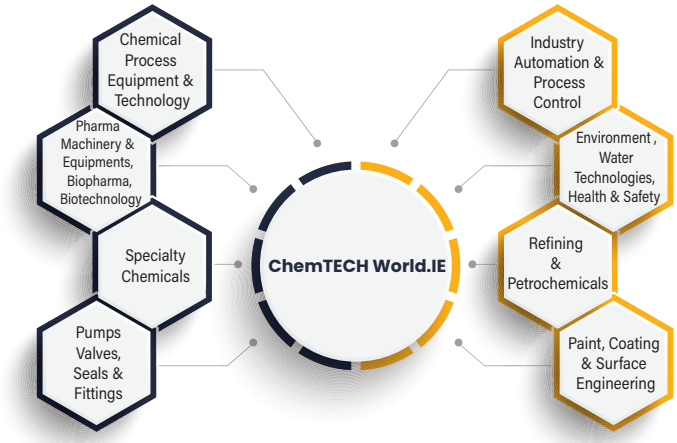

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