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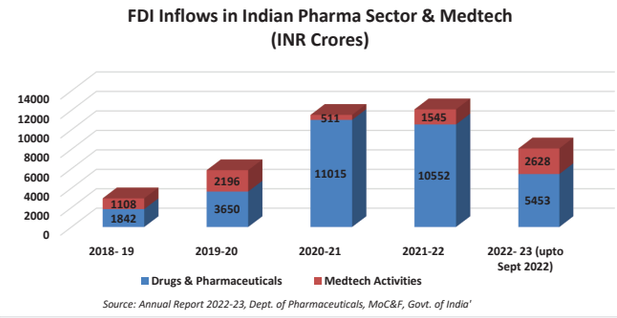
Pharma amongst the top ten attractive destinations for FDI



Source: Annual Report 2022-23, Dept. of Pharmaceuticals, MoC&F, Govt. of India'

New Delhi, India: Pharmaceutical sector has emerged as a favorite destination for the foreign investors and is one of the top ten attractive sectors for foreign investment in India. The Government has put in place an investor-friendly Foreign Direct Investment (FDI) policy to promote investment in the Sector. 100% foreign investment is allowed under automatic route in Medical Devices. In pharmaceuticals, up to 100% FDI in Greenfield projects and up to 74% FDI in brownfield projects is allowed under the automatic route. Foreign investment beyond 74% in brownfield projects requires Government approval. After the abolition of the Foreign Investment Promotion Board (FIPB) in May 2017, the Department of Pharmaceuticals has been assigned the role to consider the foreign investment proposals under the Government approval route.

Apart from this, the Department considers all FDI proposals of the pharmaceutical sector and medical devices sector wherein investors/ultimate beneficiaries in the investment proposals are from the countries sharing land border with India. The sector contributes about 3.71% of total FDI inflows in the country across various sectors. Total FDI inflows in Pharma and Medtech Sectors have been ₹ 1, 32 , 568 crore from April 2000 to September 2022. During the financial year 2022-23 (till December 2022), Department of Pharmaceuticals approved 13 FDI proposals that would result in foreign investment inflow of ₹ 2,814 crore in the brownfield projects of pharmaceutical sector.

Global Market for Medicines to Rise to USD 1.9 Trillion by 2027

N.C, USA: According to IQVIA's report Global Use of Medicines 2023 – Outlook through 2027 released early this year total spending and global demand for medicines will increase over the next five years to approximately USD 1.9 trillion by 2027. Underlying growth rate of 3-6% in spend will be driven by new drug launches and wider use of recently launched brands despite efforts by payers to constrain their budgets, and the impact of lower cost options. "COVID-19 continues to have an impact on pharmaceutical markets globally, and is estimated to continue expanding the pharmaceutical market through 2027, largely due to vaccines," said Murray Aitken, Senior Vice President and Executive Director of the IQVIA Institute for Human Data Science. "However, there are significant uncertainties in the years ahead with the transition of the global COVID-19 pandemic to a new phase where vaccines and therapeutics are available but are used inconsistently."

Medicine use, measured in defined daily doses - grew by 36% over the past decade, driven by increased access to medicines. However, growth is projected to slow through 2027 and reach a total of more than 3.4 trillion doses, up about 8% from the 2022 level. Highest volume growth is expected in Latin America, Asia and Africa, driven by a mix of population growth and expanded access, while North America and Europe will see very low growth. Per capita medicine varies by region with Japan and Western Europe having more than double the use of most other regions.

Outlook for 2027

- Market size: USD 1.9 trillion
- Medicine use : 8% growth above 2022 levels, to increase to 3.4 trillion doses
- Latin America, Asia and Africa to drive highest demand in volume
- Net cumulative pharmaceutical market to expand by USD 500 billion from 2020 to 2027, vaccines to have a major share.
- Specialty medicines to represent about 43% of global spending
- Global spending on cancer drugs expected to reach USD 370 billion
- Immunology spending growth will slow to 3-6% through 2027
- New therapies for rare neurological disorders to drive spend in neurological medicines.
- Biotech to represent 35% of spending globally

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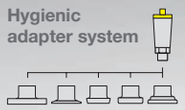

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Looking Forward VEGA

The global medicine market, using invoice price levels — is expected to grow at 3–6% CAGR through 2027 to about USD 1.9 trillion with diverging trends by region. Growth in developed economies continues at relatively steady rates with new products offset by patent expiries; Latin America, Eastern Europe and parts of Asia are expected to grow strongly from volume and greater adoption of novel medicines.

COVID-19 continues to have an impact on pharmaceutical markets globally and is estimated to expand the net cumulative pharmaceutical market by USD 500 billion from 2020 through 2027, mostly linked to vaccines. Disruptions in demand for many other medicines, due to delayed diagnoses, continue to play out although global market growth is forecast to return to pre-pandemic projected levels by 2024. All regions around the world have exceeded previously projected first-wave vaccination rates while booster utilization is lagging. This creates substantial uncertainty about the future of the pandemic and the potential risks of reemergence of infections, especially in regions of the world with the lowest immunization and booster rates.

Specialty medicines will represent about 43% of global spending in 2027 and 56% of total spending in developed markets. Global spending on cancer drugs is expected to reach $370 billion by 2027, with growth accelerating from the launch and use of novel drugs and limited new biosimilar impact. Immunology spending growth will slow to 3-6% through 2027 from price reductions associated with biosimilar competition as volume growth continues at 12% annually. New therapies for rare neurological disorders, Alzheimer's and migraines are expected to drive spending growth in neurology. Biotech will represent 35% of spending globally and will include both breakthrough cell and gene therapies, as well as a maturing biosimilar segment. Major advances are expected to continue, especially in oncology and immunology. The outlook for next-generation bio-therapeutics includes a definitively uncertain range of clinical and commercial successes.

Government of India commits to enable sustainable, affordable & easy access to diagnostics.

New Delhi, India: The Department of Pharmaceuticals, Government of India, FINDand Unitaidco-hosted a high-level meeting to strengthen cooperation to enable sustainable development and manufacturing of effective, quality and affordable diagnostic countermeasures prior to the G20 second health working group meeting in Goa. Representatives of government of India, Australia, France, United Kingdom, Indonesia, Russia, Brazil and observers Mauritius, Netherlands, Oman, international organizations and over 20 diagnostic manufacturers from 13 countries attended the meeting & 2 day workshop. During the inauguration, S Aparna, Secretary, Department of Pharmaceuticals said, "The centrality of diagnostics extends far beyond testing for a pandemic. Diagnostics are key to preventing and treating diseases optimally, and by extension achieving Universal Health Coverage (UHC). The Government of India is committed to ensuring quality, affordability and access to diagnostics." Regional development of diagnostics products through region-appropriate research and decentralized production of diagnostics can help reduce disparities, enhance health security, including pandemic prevention, preparedness and response capabilities, support UHC and contribute to regional economic growth.

Sanjay Sarin, Vice President of Access at FIND articulated, "The pandemic has bolstered the role of a more decentralized model for manufacturing diagnostics, one that combines global and regional manufacturing alike, in support of equitable and sustainable access to diagnostics worldwide. In line with the priorities of the G20, we believe that decentralized manufacturing supports the broader mission of expanding access to diagnostics and achieving UHC."

The workshop focused on the development, manufacturing and commercialization of tests for low- and middle-income countries (LMICs), and the need to accelerate regional production of diagnostics in LMICs. It provided an opportunity for diagnostic manufacturers to deliberate on the enabling factors required for the sustainability of decentralized diagnostic R&D and manufacturing. The manufacturers have evinced interest in establishing partnerships to facilitate the transfer of technology, know-how, and capacity building. Manufacturers also highlighted the need for countries to develop national diagnostic strategies with concrete budget allocations and procurement frameworks prioritizing sourcing of regionally manufactured tests. They stressed upon the need for governments as well as development partners to continue strengthening regulatory mechanisms and to make clear commitments to facilitate harmonization and fast-track regulatory processes for regionally manufactured products. In line with the India G20 Presidency goals, the participants emphasized that funding needed to be made available to create and maintain capacity for coordinated global manufacturing, R&D and technology transfer.

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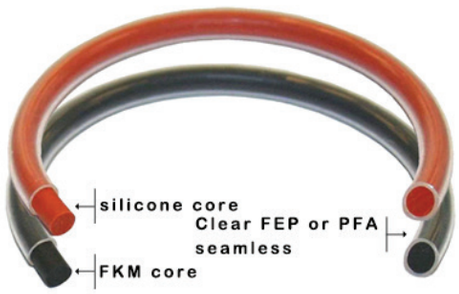

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Ipca Labs to buy stake in Unichem

Bengaluru, India: Ipca Labs, manufacturer of Pacimol, paracetamol tablets has recently announced buying 33,38% stake in Unicehm Laboratories for the value of USD 126.26 million. Ipca manufactures active pharmaceutical ingredients (APIs) and Unichem is branded generic drugs producer. In a written statement, Unichem's board will approve the appointment of three nominees of Ipca as additional directors. Ipca will launch an open offer for Unichem shareholders to buy additional 26% stake.

Cadila Pharma to set up pharma injectable manufacturing facility in Russia

New Delhi, India: Dr S Jaishankar, Minister of External Affairs, Government of India met Denis Manturov, Deputy Prime and Minister for Industry & Trade for Russian Federation for the bilateral industrial roundtable – India Russia Business Dialogue to explore the possibilities for synergistic partnerships and investments in the field of healthcare. In his address, Raj Prakash, President Corporate Affairs, Cadila Pharmaceuticals announced the group's plan to set up state of the art pharmaceutical injectable manufacturing unit in Russia to offer affordable solutions to the country USD 30 billion healthcare market. Sergey Cheremin, Chairman of the Board of the Business Council for Cooperation with India and Minister of the Department of Foreign Economic Activity and International Relations, Moscow City Government also attended the meeting held in New Delhi.

GSK's respiratory syncytial virus older adult vaccine candidate gains positive European Medicines Agency CHMP opinion

London, UK: GSK plc has announced, European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion by consensus recommending approval of GSK's respiratory syncytial virus (RSV) vaccine candidate for the prevention of lower respiratory tract disease (LRTD) caused by RSV in adults aged 60 years and older. This is the first time an RSV vaccine candidate for adults has gained a positive opinion, one of the final steps in the marketing authorization procedure prior to approval by the European Commission. There are no RSV vaccines or specific treatments currently available for older adults. RSV causes over 270,000 hospitalizations and approximately 20,000 in-hospital deaths in adults aged 60 years and older each year in Europe.1 If approved, GSK's candidate has the potential to be the first vaccine available to help protect older adults from RSV disease. GSK's marketing authorisation application has been reviewed under accelerated assessment. This applies to products determined by the CHMP to be of major interest for public health and therapeutic innovation. The European Commission's final decision is expected by July 2023.

RSV is a common contagious virus affecting the lungs and breathing passages. It is one of the major remaining infectious diseases for which there is currently no vaccine or specific treatment available for adults. There are currently no RSV vaccines approved anywhere in the world. A clinical trial that aims to expand the population who may benefit from RSV vaccination into adults aged 50-59, including participants with underlying comorbidities, is fully recruited. Results are expected in 2023, together with additional results from the AReSVi-006 phase III efficacy trial and the AReSVi-004 immunogenicity trial. These trials continue to evaluate an annual revaccination schedule and protection/ immunogenicity over multiple seasons following one dose of the RSV vaccine candidate. Results from two additional influenza vaccine co-administration trials are also expected in H1 2023.

GSK's RSV older adult vaccine candidate contains a recombinant subunit RSV prefusion F glycoprotein antigen (RSVPreF3) combined with the Company's proprietary AS01E adjuvant. Across multiple trials, the vaccine candidate was generally well tolerated with an acceptable safety profile. The most frequently observed solicited adverse events were injection site pain, fatigue, myalgia, and headache. These were typically mild to moderate and transient. The GSK proprietary AS01 adjuvant system contains QS-21 STIMULON adjuvant licensed from Antigenics Inc. a wholly owned subsidiary of Agenus Inc.

Cipla signs licensing agreement for Galvus

New Delhi, India : Drug major Cipla has signed licensing agreement with Swiss major Novartis Pharma AG to produce and market Galvus & Galvus combination range of products used in type 2 diabetes treatment from 1st January 2026. Galvus is one of leadng brands in oral medication in Dipeptidyl - Peptides - 4 (DPP4) category. The deal will strengthen the position of Cipla in market for diabetes medication. The agreement is subject to satisfaction of certain conditions precedent according to Novartis.

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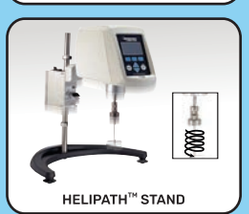
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Zydus granted FDA approval for azithromycin

Ahmedabad, India: The US Food and Drug Administration (FDA) has granted final approval to India-based Zydus Lifesciences' 500mg azithromycin tablets. The company will manufacture tablets in formulation facility in Moraiya, Ahmedabad. Azithromycin is used to treat like bronchitis, pneumonia, sexually transmitted diseases (STDs) and infections of the ears, lungs, sinuses, skin, throat and reproductive organs.

Stability of input costs and specialty product launches to support performance of Indian pharmaceutical companies in FY2024: ICRA

Gurgaon, India: ICRA expects the revenues of its sample set of 16 Indian pharmaceutical companies to grow by 6-8% in FY2024, primarily driven by steady performance across key markets (the US and India) and some recovery in growth in the European market. The operating profit margin (OPM) is expected to be steady at 21-22% in FY2024, supported by stabilization of raw material prices and increased focus on complex generics/specialty molecule launches in the US market.

Commenting on the growth drivers, Deepak Jotwani, Assistant Vice President & Sector Head, ICRA, said, "New specialty/complex generic molecule launches in the US market by ICRA's sample set of leading pharmaceutical companies will help them offset continued pricing pressure and also support revenue growth of 6-7% in FY2024. As for the domestic market, ICRA expects the revenue growth for its sample set to increase to 6-8% in FY2024, post an estimated growth of 3-4% in FY2023, given the large base of FY2022. Structural factors such as an ageing population and continued rise in lifestyle/chronic diseases, in addition to the WPI-linked price hike for products under the NLEM, new product introductions, and annual price hikes for non-NLEM products are expected to support revenue growth for the industry. Steps being taken by sample set companies towards new product introductions and enhancement in field force are also expected to support their growth going forward."

While India and the US remain the key focus markets for Indian pharmaceutical companies, most companies have also enhanced their presence in emerging markets to fuel their growth. Growth in the emerging markets has been driven by new product launches, strong demand, and depreciation of the INR against certain currencies. Mergers and acquisitions (M&A) in the pharmaceutical industry have picked up considerably over the past year. Leading Indian pharmaceutical companies have made sizeable acquisitions in the recent past to enhance market share in select geographies/therapeutic areas, primarily in the US and the Indian markets, which are expected to provide diversification benefits and support revenue growth for these players going forward. However, the sizeable value of most of these M&A deals also indicates the elevated risk appetite of these pharmaceutical companies.

As for FY2023, ICRA now expects the revenues for its sample set to grow by 6-8% (against the earlier expectation of 4-6%), closer to ~7.7% growth in FY2022. The same will be supported by 10-12% growth in the US market (driven by robust performance of new product launches including first-to-file molecule, Lenalidomide) in addition to the depreciation of the INR by ~8% against the USD during fiscal, while the revenues from the European market are expected to contract marginally, given the ongoing macroeconomic challenges and the large base of the previous fiscal, which was supported by Covid-19 vaccine sales. The OPM is projected to contract by 50-100 bps to 21-22% in FY2023 due to relatively high input costs in H1 FY2023.

ICRA expects the R&D expenses for its sample set to stabilize at around 7-7.5% of their revenues as companies will optimize their spend, focusing more on complex molecules and specialty products, against generics. Moreover, the annual capex run rate is expected to be maintained at Rs. 15,000 crore in FY2024. ICRA maintains its Stable outlook on the pharmaceutical industry, led by expectations of continued steady revenue growth and comfortable profit margins for its sample set. The return indicators (RoCE of 14-15%), capital structure, liquidity profile, and coverage indicators (Total Debt/OPBDITA of 0.9-1.0 times) are expected to remain comfortable, through strong internal accruals. ■

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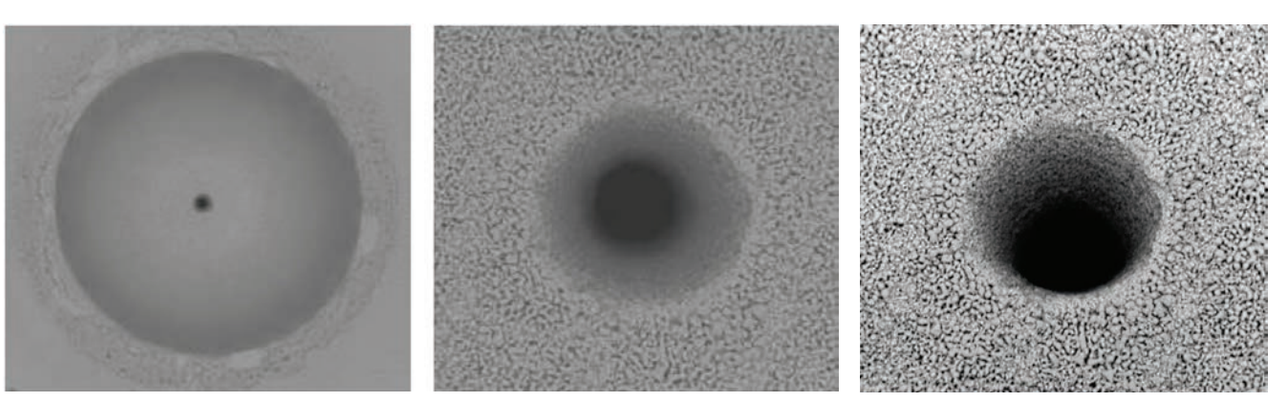
Quality Assurance in Health Technology

Innovative solutions are needed to quickly and cost-effectively check the required hygiene and quality standards in order to ensure access to high-quality, safe medical and pharmaceutical equipment in the future. Various essential quality and stability tests are already carried out during the manufacturing and processing process of products such as syringe cylinders, vaccine vials or infusion and transfusion bags. Thereby, the control mechanisms used have to reliably detect even the smallest variation and damage in the material, to exclude contamination in the context of the application. Therefore, GFH GmbH offers manufacturers of medical and pharmaceutical products a laser-based solution. A cost- and time-saving opportunity is offered to validate this quality test, which works particularly flexibly and gently on materials by drilling high-precision leak holes of just 5 µm to 50 µm diameter into individual specimens of a production line. While the hole sizes can be kept very accurately, no cracks or pressures will arise around the drilling site.

Scanning electron microscope images of the leakage hole

As a result of the ongoing pandemic the demand especially for so-called 'leakage drilling' in Syringe cylinders increases rapidly. During manufacturing, these deliberately selected samples are intended to exclude defects in the material of the vials and cylinders for example to prevent subsequent contamination of the transfusion or leakage during usage. Increasing demand for such control procedures is due not least to global vaccination campaigns and the associated increased demand for flawless medical and pharmaceutical products. Manufacturers therefore need reliable methods that can carry out random quality check with high precision in a time- and cost-saving way. For this purpose, laser technology is a predestined method due to its very precise and non-contact processing beam, which is why some well-known manufacturers have already approached GFH GmbH regarding the generation of leakage drills.

The Bavarian laser experts have developed a process, which allows the drilling of high-precision leak holes validating the control mechanisms used in production without much effort. The resulting (defective) products with micro drill holes are then integrated into the manufacturing process of the medical device manufacturers. These ´prepared´ products then form the control group for the quality- and leak test. "The ultrafast laser serves as an excellent tool to equip the glass vials



Scanning electron microscope images of the leakage hole

Leakage drilling in glas

with leakage holes which are very small and precise, but still do not damage the material around the drill hole", explains Andreas Reitberger, Sales Manager at GFH GmbH. "There are numerous reasons for this: on the one hand, the ultrafast laser pulses that hit the material prevent tensions and cracks in it by means of so-called "cold ablation". On the other hand, there are no limits to the variety of materials used in laser processing. This enables even hard-to-machine materials such as glass or special medical plastics to be processed with high precision." ■

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Why Pharmaceutical Manufacturers Should Embrace Machine Learning – Now

Figure 1: Pharmaceutical companies have an unprecedented need for operational excellence.

The manufacture of pharmaceuticals is a highly regulated and complex process. Patented products are licensed for a finite amount of time before they become generic, equating to a constant sense of 'the race is on' to be able to meet demand.

Now, possibly more than ever before, these businesses globally have an intense focus on reducing supply chain disruption, increasing capacity of batch production and reducing batch losses. Reducing lifecycle maintenance costs and CAPEX remain high on the agenda too.

Notwithstanding compliance and safety, manufacturing equipment availability is therefore a top priority. Without exception, pharma manufacturers tell us that they want to be able to predict asset degradation and failure well in advance of an impending breakdown or disruption to be able to make decisions that can minimize cost and disruption.

Simplicity – high accuracy, fewer false positives

Today's machine learning solutions allow pharma manufacturers to achieve fast results without needing to write a single line of code. The data science is hidden and allows 'normal' workers to manage them. Current staff, already employed, can be easily taught and trained to manage the platform. The number of "qualified" users is therefore very high, enabling engineers to solve their own engineering problems!

In many industries data is unpredictable. It has anomalies, there is a danger that you can be sent unwillingly down the wrong path.

Pharma, however, has very little, if any 'crazy data.' Why? Because by its very nature, the process of manufacturing drugs is hyper-controlled. The adoption of machine learning can bring rapid results and value to pharma companies within weeks.

Scalability – failure signatures transferable across assets

The pharma industry also has pools of similar equipment, such as the same pumps used in multiple services, or several of the same packaging lines. This is where transfer learning comes in to its own. By sharing the normal and failure behaviours of assets that we find on one machine with the other members of the pool, we can rapidly increase the scale, safety and prevent breakdown of all equipment of the same type and configuration. This ability to rapidly scale an enterprise can create millions of dollars in value.

Figure 2: Now is the time for pharmaceutical manufacturers to accelerate their approach to digital transformation and machine learning solutions.

Speed – faster results as no asset model required

One example that demonstrates such results can be found at a large-scale pharmaceutical plant, where several large chillers and compressors are critical equipment infrastructure. Despite all six sigma efforts, failures were still causing enormous losses. Aging equipment, increasing energy usage, higher maintenance and inadequate equipment health status reporting contributed to the problem. Aspen Mtell's industrialized machine-learning reversed the situation. Autonomous agents turned corrective and preventive maintenance into prescriptive maintenance. These agents now advise when equipment should be maintained with early warning of impending failures. This gives sufficient notice for orderly, rapid problem correction at the lowest cost. Overall production has improved dramatically.

In another application, AspenTech's Aspen Mtell solution was used to determine the early signs of seal failure through learning of similar patterns from live equipment. It was also focused on continuously learning new events (normal and abnormal) together with additional late stage indicators, providing a confidence increase in seal change decisions. The result was a decrease in the frequency of the need to make mechanical seal replacements, leading to a lessening of supply chain disruption; a reduction in lifecycle maintenance costs of 60%, and a reduction in CAPEX and associated lifecycle costs of 50%.

Across the pharmaceuticals industry today, the latest asset performance management (APM) solutions are enabling pharmaceuticals companies to protect their supply chain, increase asset utilization and avoid unplanned downtime by accurately predicting when equipment anomalies will occur, understanding why they do, and prescribing what to do to avoid a potential failure. Given today's volatile and challenging marketplace, it is exactly the right time for pharmaceutical manufacturers to act to accelerate their approach to digital transformation and machine learning solutions.. ■

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Dry Vacuum Technology for Chemical & Pharmaceutical Processes

Vacuum plays an essential role in chemical and pharmaceutical processes. Whether in vacuum conveying, inertization, distilling or drying processes, vacuum is used everywhere to make processes safer, faster and more economical or to make them possible in the first place.

The various technologies for generating vacuum are versatile. Liquid ring vacuum pumps and steam ejectors have been the robust workhorses for many decades when it comes to generating vacuum. However, like rotary vane vacuum pumps with recirculating oil lubrication, they have one disadvantage: they require an operating fluid that comes into contact with the process gas. In the mid-1990s, Busch Vacuum Solutions launched the first screw vacuum pump on the market, the COBRA. The major difference to the vacuum pumps known at that time was that screw vacuum pumps did not require any operating fluid to compress the process gas. This is why they are called "dry" screw vacuum pumps (Fig. 1). Dry screw vacuum technology is now also widely used in the chemical and pharmaceutical industries.

Function

In a screw vacuum pump, two interlocking screw-shaped rotors rotate in opposite directions (Fig. 2). The process gases are drawn in, trapped between the cylinder and screw chambers, compressed and transported to the gas discharge. During the compression process, the screw rotors do not come into contact with each other or the cylinder. Precise manufacturing and minimal clearances between the moving parts enable this operating principle and, in addition, ensure a low ultimate pressure of up to 0.01 millibar (absolute).

COBRA screw vacuum pumps operate with a cooling system which ensures even heat distribution, greater thermal efficiency and stability throughout the pump body. This allows the temperature to be selected so that it is high enough not to condense the process gas but low enough to avoid potential temperature-related problems such as gas deposition or spontaneous ignition. The absence of operating fluid allows a compression of the process chamber without contamination or reaction.

Protecting the vacuum system

Depending on the process gas, the vacuum pump can be exposed to certain risks. It is therefore important that the process gases are sufficiently known to minimize these risks. Different components are often required, which can be installed on the inlet or pressure side, in order to convey the process gas without damaging the vacuum pump. This is called a vacuum system, which can also consist of several vacuum pumps (Fig. 3).

For safe operation of the vacuum system, it is important to protect it from corrosion and deposits caused by crystallization or polymerization, and to increase the material resistance.

Protection against corrosion

Various measures can be effective in protecting the vacuum system or the individual vacuum pumps against corrosion. The first possibility is to prevent corrosive substances from entering the interior of the vacuum pump. This can be implemented by upstream condensers or gas scrubbers.

The second possibility to avoid corrosion is to keep the process stream in the gas phase. In a screw vacuum pump this can be implemented by setting a certain operating temperature. In addition, the process gas can be diluted by a supplied ballast gas to reduce the partial pressure of the condensable gases. So, the following simple logic applies: suction in gaseous form and ejection in gaseous

form. The minimum temperature must therefore be selected so that it is high enough to prevent gases from condensing out. The maximum temperature must be selected so that the vacuum pump is not damaged or so that the maximum permissible temperature according to ATEX classification is not exceeded.

A third possibility is to use compatible materials for the vacuum pump. In COBRA screw vacuum pumps from Busch Vacuum Solutions, for example, all parts in contact with the process are made of ductile cast iron by default and have a special coating that is resistant to almost all chemicals.

Protection from particles entering the system

Screw vacuum pumps should always be operated with an inlet screen or an inlet filter. This is to prevent particles from entering the inside of the vacuum pump. Due to the precise manufacturing of screw vacuum pumps with the associated small clearances and tolerances, there is a certain sensitivity to entrained particles. Dry screw vacuum pumps are frequently used with particulate dryers, especially in the pharmaceutical industry. A certain number of such particles can easily pass through the vacuum pump together with the process gas or be flushed out at the end of the process. Nevertheless, it is advisable to take appropriate precautions in order to prevent particles from being sucked in on a regular basis. For example, Busch offers a large number of different particle filters for every application.

Leak-tightness of the vacuum pump/ vacuum system

Vacuum pumps and vacuum systems in a chemical environment must be so tight that no or still a minimum of ambient air can enter and create a potentially explosive atmosphere, or toxic or explosive gases can escape. Polymer o-rings are generally used to prevent leaks between two stationary parts. The resistance depends on the selected polymer. The seal material therefore also needs to be adapted to possible process gases. Busch Vacuum Solutions has had a dynamic sealing concept for rotating shaft feedthroughs certified by TÜV SÜD in accordance with the Technical Instructions on Air Quality Control (TA Luft). These seals are considered technically leak-tight.

Tips for operation

For most applications it is recommended that the vacuum pump is warmed up for a certain lead time before process operation. This allows the specified temperature to be set. After the end of the process, it is recommended to purge the vacuum pump with non-condensable inert gas to completely remove the process gas from the vacuum pump before switching it off. Nitrogen is normally used for this flushing process. Flushing the vacuum pump with a cleaning liquid at the end of the process is also possible and recommended if there is a risk of deposits forming inside the vacuum pump during cooling.

Explosion protection

With different sealing systems, various coatings and appropriate accessories, COBRA screw vacuum pumps from Busch can be configured to be compatible with virtually any chemical. In addition, various ATEX versions are available for COBRA screw vacuum pumps in accordance with EU Directive 2014/34/EU. Also, any other national regulation can be adapted for these vacuum pumps like EX-proof in US or KOSHA in South Korea. This means that these vacuum pumps can also be used worldwide in potentially explosive areas and for conveying explosive gases and vapors. Flame arresters may also be integrated if necessary. ■

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Government Initiatives, Market Conditions to Propel the Indian Pharmaceutical Industry

India is on a continuous growth trajectory towards becoming a global leader in pharmaceutical manufacturing. Globally, India ranks third in terms of pharmaceutical production by volume and 14th by value. The Indian pharmaceutical exports are valued at around $24 billion, and the domestic market is estimated to reach $71 billion by 2025 from $42 billion in 2021, according to India Brand Equity Foundation (IBEF).

India is one of the top suppliers of bulk drugs and formulations globally and has the highest number of US FDA-approved plants with state-of-the-art technologies. India supplies a majority of generic drugs globally to the US, UK, and several developing nations. India provides almost 40% of the total American generic drug demand and addresses nearly 25% of the total drug demand in the UK. According to Institut Montaigne, India also accounts for 60% of global vaccine production, contributing 50% of the WHO demand.

This success can be attributed to the advanced capabilities in formulation development, entrepreneurial ability, low manufacturing cost, government initiatives, and the industry's vision to establish India's footprint in large international markets. Contract research and manufacturing services and the biotech industry are the two fast-growing biopharmaceutical industry segments globally. Our analysis indicates that the global contract manufacturing services market was estimated at $109 billion in 2020, with the Indian sector valued at around $6.8 billion. Contract manufacturing contributes up to 60% of formulations and bulk drug manufacturing and presents a significant growth opportunity. India is also moving towards innovation, with around 95 biosimilars approved to date. According to Frost & Sullivan's analysis, the biosimilars global market is estimated to be at $35.7 billion in 2021, with India capturing a market share of 1.7%. It is expected to grow at a compound annual growth rate (CAGR) of 34% in the next five years. The pharmaceutical industry will see a new wave of patent expirations between 2021 and 2026, leading to biosimilars, bio-betters, and bio-generics development.

Indian CROs are becoming more involved in developing biosimilars due to their expertise in streamlining biological products' research, development, manufacturing, and up-scaling. Indian vaccine manufacturers have emerged as significant players in the global market. India has been a substantial supplier of basic Expanded Programme on Immunization (EPI) vaccines to UNICEF. They currently produce new and more complex vaccines for meningitis, Haemophilus influenza Type B, rotavirus, influenza A (H1N1), and pneumococcal conjugate vaccines. The introduction of new vaccines in the Universal Immunization Program (UIP) is expected to promote investment and R&D in the vaccines sector in India. COVID-19 has also boosted the industry, resulting in the manufacturing of COVID vaccines for domestic use and exports. However, India lags in the active pharmaceutical ingredients (APIs) and bulk drug manufacturing segment. India imports around 68% of its API consumption by value from China and is highly reliant on China for fermentation-based APIs (antibiotics), feedstock, and many key starting materials (KSMs). With COVID-19 creating several challenges like restrictions on exports and imports, supply chain, and logistic issues, India's pharma sector is trying to reinvent itself and move forward from its long-standing dependence on the export of generics towards enabling the industry to become an end-to-end drug manufacturer. This includes a parallel thrust on localizing API and bulk drug manufacturing. Impact of Government Initiatives Amidst the pandemic, India has also seen a spurt in the growth of start-ups working towards accelerating lowcost development systems by leveraging the government's schemes like Make in India and Atmanirbhar Bharat. India has gained a significant

competitive advantage as the cost of manufacturing in India is around 40% lower compared to the USA.

The Indian government has also set up a production-linked incentive (PLI) Article The Global Growth Pipeline Company package focusing on APIs and the API Parks scheme to boost the competitiveness of India's manufacturing and promote domestic manufacturing of critical intermediates and APIs. In March 2020, the government approved the $1.4 billion (₹10,000 Crore) PLI scheme to reduce India's dependence on China for raw materials and locally produce crucial antibiotics, anti-HIV drugs, vitamins, and cardiovascular diseases.

The Union cabinet cleared the new PLI scheme for the domestic pharmaceutical sector for 2020-21 to 2028-29. The scheme is expected to provide about $2.04 billion (₹15,000 crores) in incentives. This scheme expects total incremental sales of $41.2 billion (₹2.94 trillion) and incremental exports of $27.5 billion (₹1.96 trillion) from 2021 to 2029. In May 2021, the Department of Pharmaceuticals (DoP) issued revised Guidelines for the PLI scheme to promote domestic manufacturing of critical KSMs, drug intermediates, and APIs in India. The new PLI scheme is expected to boost the existing brownfield API units in the country and bring 20 priority molecules to be produced with scale; thereby, decreasing dependency on China. Additionally, under the Atmanirbhar Bharat 3.0, the government announced Mission COVID Suraksha to accelerate the development and production of indigenous COVID vaccines. In May 2021, to augment the capacity of the indigenous output of Covaxin under the mission, the Department of Biotechnology, Government of India provided financial support in the form of a grant to vaccine manufacturing facilities for enhanced production capacities, which is expected to cross ten crore doses per month by September 2021.

Bright Future Ahead for Indian Pharmaceutical Industry

World-class capabilities and market conditions ensure that India remains one of the most lucrative pharma markets in the world. India is already an attractive destination for manufacturing pharmaceuticals due to its robust capabilities across the value chain. In the future, pharmaceuticals manufacturing in India has multiple opportunities for growth across formulations, bulk drugs, indigenous vaccines manufacturing, and contract manufacturing. Frost & Sullivan's analysis indicates that the Indian pharmaceutical industry is at the forefront of the Make in India initiative. Over the last few decades, the industry has experienced rapid growth. India has demonstrated commitment to ensuring affordable and accessible medicines globally, and most of the domestic demand for drugs is fulfilled by medicines made in India.

Many opportunities exist in the core businesses (formulations and bulk drugs) and new companies (e.g., complex generics, vaccines) that present a favorable outlook for the industry over the next 10-15 years. Despite the unprecedented times, the industry is working in close collaboration with the government to continue growing as the leader of pharmaceutical manufacturing and become the 'pharmacy of the world.' ■

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One-Pot Batch-mode Synthesis – A Veritable Challenge to Continuous-mode Synthesis

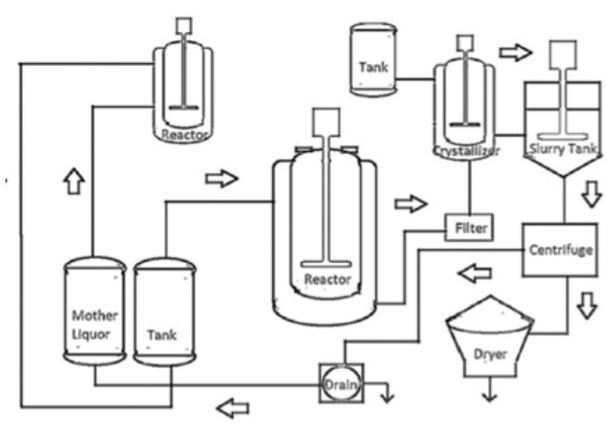
Batch-mode synthesis is the most adopted route in the Chemical and Allied Industries the world over; these industries include Bulk Drugs/APIs, Drug-Intermediates, Fine Chemicals, Speciality Chemicals, Agro-Chemicals (including Pesticides & Insecticides) & Dyes and Dye-Intermediates. Here, each step in the synthesis is characterized by a Unit Operation and the equipment that executes the step is unique in its ability to perform the desired unit operation.

Since its inception, the process industry has embraced batch-mode synthesis centred around unit operations because of their identity with lab-scale synthesis and utter simplicity and naturally enough, plant-scale technologies have evolved around these unit operations; with every advancing generation, scientists and researchers worked towards technology upgradation in each of the established unit operation steps in the synthesis of the chemical. So much so that it is still inconceivable, today, to think of setting up a new Chemical Plant without enumerating the unit operations in the production route to be adopted and identifying the equipment (for investment in) that will optimally fulfil the processing needs to profitably reach the products to their respective markets.

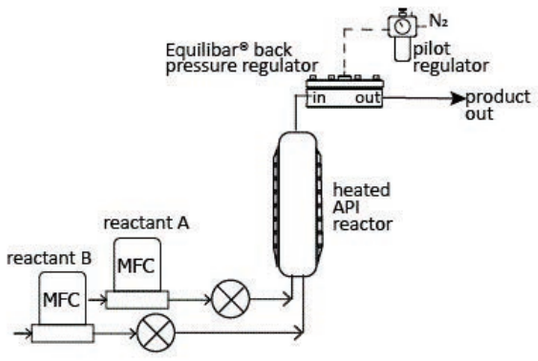
Over the years, an alternate synthesis route, founded on the principles of Flow Chemistry, has received increasing attention. While this alternative route also recognizes the fact that synthesis of most chemicals follow definitive steps that are also characterized by Unit Operations, the manner in which it executes these steps fundamentally differs from that adopted by a batch-mode of synthesis, essentially in the time dimension, while the rest of the process parameters of pressure, temperature, stoichiometric composition, concentration etc governing each step largely tend to remain consistent with that of the batch mode, with some caveats. Flow Chemistry technology is still evolving. It must however be noted that, given the state of this technology today, Flow Chemistry has been successfully adopted in the synthesis of only a few chemicals. It is not viable in situations where, for example, the product is a low volume product, or a company needs to switch to synthesis of many products every month. A high-volume product, as of now, appears to be better suited for adoption of Flow Chemistry in its synthesis. If viable, it then becomes a dedicated line for that product.

The figures below give a basic picture of the batch-mode and continuous-mode (Flow Chemistry based) of chemical synthesis.

The conventional advantages of Batch-mode synthesis remain its main attraction and economies of scale continue to justify its large-scale adoption in the Indian Process Industry. Synthesis consists of one or more Reaction(s) together with associated Work-ups / Purifications steps and usually requires several independent and distinct steps. Each step is usually carried out in a separate equipment. This results in multiple transfers of intermediate masses between equipment. Also, quality parameters at the beginning / end of most of these discrete steps are defined to help ensure repeated achievement of consistency in quality of the end product. However, in industries such as Bulk Drugs/APIs and Intermediates, Speciality Chemicals, Fine Chemicals etc that cater to the requirements of regulated markets, the requirement of stringent quality adherence and associated audits have necessitated achievement of quality parameters at almost every intermediate stage



Batch-mode (Ref-1)



Continuous-mode (Ref-2)

of the synthesis. This entails requisite documentation-support that help trace quality non-performance to a particular intermediate step, in the event of failure on quality front of a product. Conforming to such defined quality parameters and the maintaining of multitudes of documentation in support of such quality conformance has remained a key sore point for the manufacturers.

Another typical feature of batch-mode synthesis has been the use of several equipment in the synthesis and work-up/purification. There are almost as many equipment involved as there are number of processing steps. It is not uncommon to notice manufacturers investing in batteries of each unit-operation equipment (like several Reactors of varying capacities, several Separation Equipment like Distillation Columns, Filters, Extractors etc, several Crystallizers / Precipitators, several Dryers etc) when setting up a plant to manufacture several products. Such a configuration invites complex equipment planning / scheduling / cleaning tasks. Associated with this complex task is the engagement of more labor, movement of material between equipment, yield loss, susceptibility to quality deviation due to contamination etc, etc. Despite these issues with Batch-mode synthesis, investment in a new Chemical Plant continues to reliant on this mode of synthesis.

In the debate, Flow Chemistry or Continuous-mode synthesis Vs Batch-mode synthesis, there is an increasing shift towards the Continuous mode internationally, on the backing of the big-league players, but the debate has only just begun and is far from over. In India too, the situation is not any different. Proponents of Continuous-mode synthesis cite certain key arguments to support their leaning. These essentially are :

- Continuous, without break, synthesis, reducing human error
- Better Quality
- Less Space
- Lower Yield loss
- Lower operating costs

While Flow Chemistry or Continuous-mode Synthesis is seeing more of industrial-scale implementation, that appear to be throwing up evidence in favour of as well as against the new Technology, more and more data is getting generated for the protagonists to work upon the shortcomings and improve the implementation criteria of this technology. The batch-mode protagonists, on the other hand, do not appear to be much concerned about the erosion in support for this long-standing, proven technology.

Time has therefore come to address this issue (shortcomings of batch-mode synthesis) in a manner that draws upon all available engineering and technology resources to mitigate the associated pain and distress attributed to the batch-mode synthesis, in a definite, consistent and wholesome manner. Batch-mode synthesis can be improved upon to match the benefits, if not exceed them, of the Continuous-mode synthesis. There is no reason to believe that, with paradigm shift

in batch-mode definition and its implementation, continuous-mode synthesis would replace the batch-mode technology in the industry yet.

We need to begin by re-visiting the synthesis of Chemicals. Chemistry has taught us that the most efficient synthesis of any chemical product is by adoption of "One-Pot Process". Since it is considered an ideal condition and therefore 'impossible' to achieve, the multi-step-multi-equipment format in synthesis found ready acceptance as the next best. We need to question this. We need to subject this hypothesis to rigorous evaluation.

'One-Pot Synthesis' & 'One-Pot Reactions' are terms commonly used, many times interchangeably. In reality, 'One-Pot Synthesis' goes beyond 'One-Pot Reactions.' In addition to Reactions, if one can do the work-ups in the same equipment then we would be closest to 'One-Pot Synthesis.' If all of work-up stages cannot be executed in the same equipment, then the next best thing would be to execute as many as possible in the equipment. Even this step, to begin with, would mean process economy and result in a far-improved batch-mode synthesis. Some of the issues with the current practice of batch-mode would have got resolved.

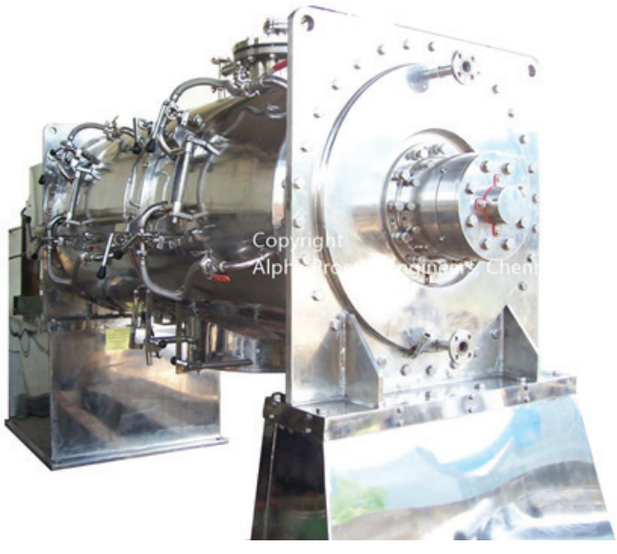
One-Pot Reactions result when one re-designs Reactions such that the desired product, requiring several Reactions in their synthesis, is obtained as a result of just one multi-step Reaction, instead of several independent Reactions. This is easily said than done. This has been researched extensively and success reported in synthesis of many molecules / chemicals. This has helped cut down on several work-up steps and save on avoidable usage of solvents. This is also said to promote 'green' chemistry.

A more significant gain can be realized if, together with this 'One-Pot Reactions', one can carry out one or more work-up/purification stages in a synthesis in the same equipment, thereby minimizing mass transfers, reducing other solvent usage, recovering solvents where used, increasing contained operations, reducing yield loss, reducing batch cycle-times and achieving greater consistency in quality of the end-product. Need for cleaning substantially reduces to cleaning fewer equipment, thus eliminating instances for cross-contamination. Production scheduling also gets simplified. This emphasizes the need to design equipment such that several unit operations, subsequent to Reactions, can be carried out in the same equipment (Reactor), with requisite controls. To achieve this, a need to re-visit the underlying principles of Extraction, Distillation, Phase-separation, Crystallization, Precipitation, Filtration and Drying becomes apparent. Theory of Reactions and Reactor Design too need to be worked upon to help re-design agitation systems to achieve optimum efficiency in the combined sequence of synthesis-steps.

One-Pot Synthesis would thus eliminate breaks (pauses) between steps, reducing occasions of human error during a batch process – an important advantage attributed to Continuous Synthesis.

More than 3 decades ago, the introduction of Filter-Dryer (eg, Rosenmund's ANFD) was the first attempt to move towards One-pot processing. Though very successful, this did not provide impetus to combine other work-up / purification steps in a single equipment. In a limited sense, where the synthesis only involved Reaction and Drying, One-pot Reactor-Dryers were introduced successfully on industrial scale. The rest of the work-up processes remained independent and separate equipment continued to be used to carry out these steps. Thus Batch-mode synthesis continued to be equipment-intensive.

Today, a paradigm shift towards batch-mode One-Pot Synthesis has already begun. M/s Alpha Process Engineers (APE) is offering 2 distinctly independent Processors that come close to delivering One-Pot Synthesis. In one version, a Reactor-Dryer is offered where Reaction and Drying unit operations can be carried out in a sequence. The Processor incorporates feature of micronization too. As a result, lump formation is broken down effectively and fine dry powder is discharged. In the same category, APE offers a Reactor-Filter-Dryer wherein, in a single sequence of operations, Reaction, Extraction,



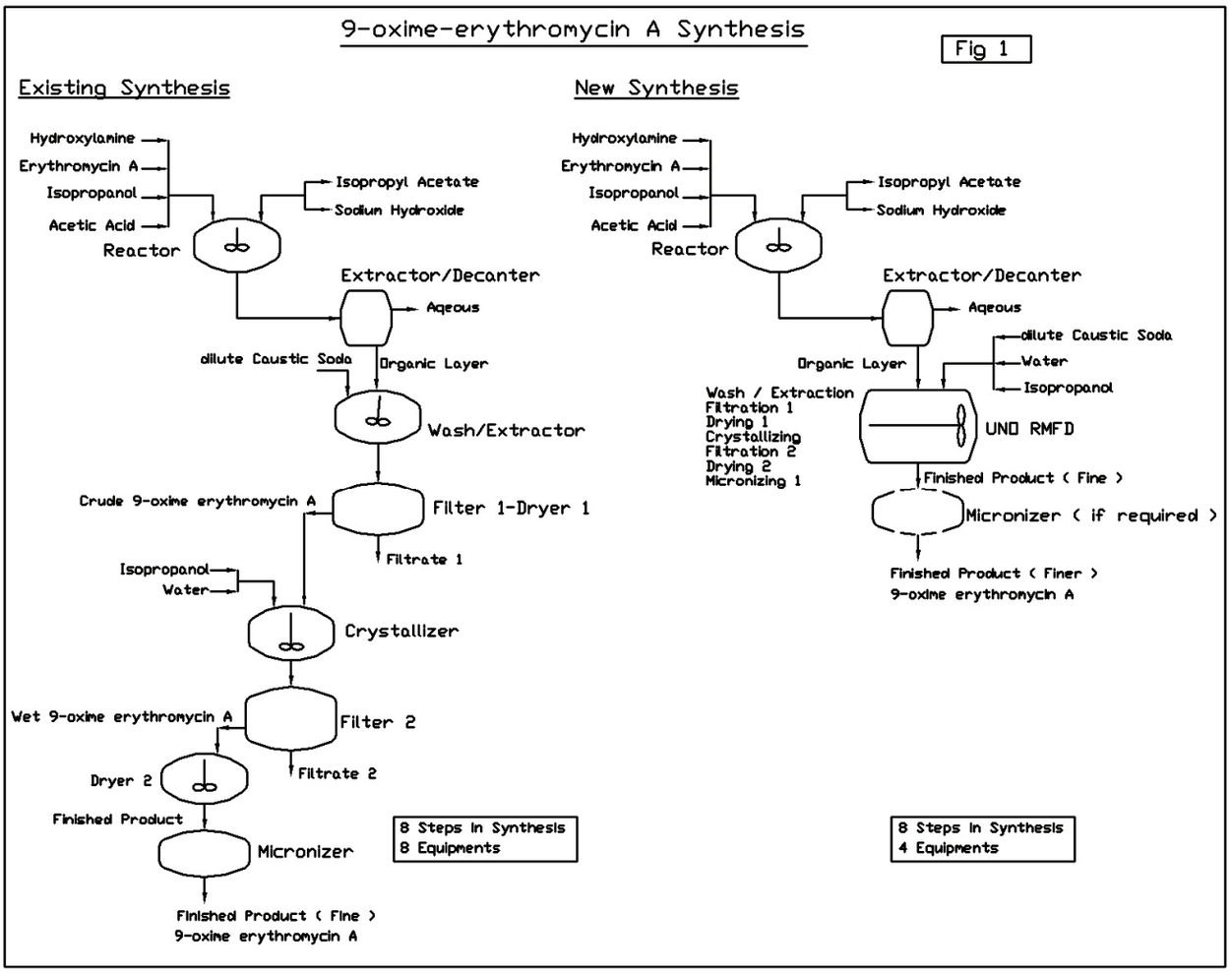


Fig. 1

Crystallization/Precipitation, Filtration, Washing, Drying and Micronization can be effectively carried out, without the product leaving the system. This would symbolize the best of containment in any synthesis.

In the second version, a combination of 3 Processors together constitute the apparatuses for total synthesis. These 3 equipment can together execute the entire synthesis. This configuration becomes essential when phase-separation becomes necessary and the lighter phase leaves the equipment first, carrying the product with it.

Typically, synthesis of an API or Drug involves more than one stage and each stage consists of Reaction followed by work-ups or purification steps. Each stage becomes a fit candidate for One-Pot synthesis. And therefore, typically, an API or Drug synthesis can be executed in a couple or minimal number of One-Pot Processors, one for each stage at worst.

When the product of a reaction stays in the solid state throughout the synthesis, the first version of the Processor finds application. This is a Reactor-Filter-Dryer, a true One-Pot Processor. When as a Reactor, the agitation system brings the reactants together very efficiently and creates conditions for quick transformation of the reactants into products. This Reactor-Filter-Dryer is of horizontal configuration. It has been found to even obviate the need for a solvent-based medium for completion of a reaction (eg, the reactants, dimethylamine hydrochloride and dicyandiamide, combine to form metformin hcl without the aid of any solvent).

The agitation system does not stop due to load during reaction, as that in the conventional, vertical configuration Reactor is prone to, in the synthesis of several organic compounds. From gentle mixing to intense, turbulent agitation, the impeller system generates appropriate conditions for efficient reaction. Every type of Reaction, be it Combination, Decomposition, Neutralization, Single-

displacement, Double-displacement, Precipitation, Redox or Combustion, is handled efficiently.

If the product of reaction does not go into dissolution during the entire synthesis, the first version of the Processor can handle the subsequent purification / work-up steps without the need to transfer the mass. Extraction, Crystallization, Precipitation, Filtration, Washing and Drying can be effectively executed in the same Processor in one appropriate sequence. This would represent a true One-Pot Processor, and the synthesis a true One-pot synthesis.

If the product of reaction enters into a liquid phase (dissolved), the second version of the Processor kicks in. Steps subsequent to Reaction cannot be continued automatically within the same Processor. Every time the product is carried into a dissolved state, it becomes necessary to separate product-carrying liquid in an external filter outside of the Processor, empty the Processor of the other bye-products and clean the Processor of residues, re-introduce the product-bearing liquid back into the Processor and complete the subsequent steps in the same Processor. A minor deviation from a literal One-Pot-synthesis, nevertheless, the complete synthesis can be completed in a minimum of 2 equipment.

Two illustrations would clarify the distinction between the two versions of One-Pot Processors introduced by APE.

In the first illustration, referring to Fig. 1, the product dissolves in a solvent / aqua medium at the end of the Reaction and leaves the Reactor, only to enter a One-Pot Processor where rest of the work-up / purification procedures are completed in a single equipment.

And in the second illustration, referring to Fig. 2, the product remains in solid state in stage 1 and 2 of synthesis and goes into solution in stage 3 of the synthesis.

In both the illustrations, the steps of synthesis (unit operations) are retained while achieving equipment economy, together with reduced space, reduced batch-cycle time, significantly improved yield, more consistent quality, reduced labor and significantly reduced production cost by adoption of One-Pot Synthesis.

APE has supplied several Reactor-Dryer versions. Applications include propionate metal salts as supplements for the poultry industry, Sodium and Magnesium Valproates and Divalproates (APIs in the treatment of Epilepsy etc) and others. The second version of One-Pot Synthesis involving a single Reactor-Filter-Dryer has been demonstrated successfully on pilot scale. Also, the 3-Processor application has been successfully demonstrated on a pilot scale for several products, including Metformin HCl for Industrial Clients. In this latter case, a batch was produced where the Reaction was carried out without solvent medium. This gave better quality end-product.

As is obvious from the two illustrations above, adoption of One-Pot Processing in batch-mode synthesis results in the following tangible benefits :

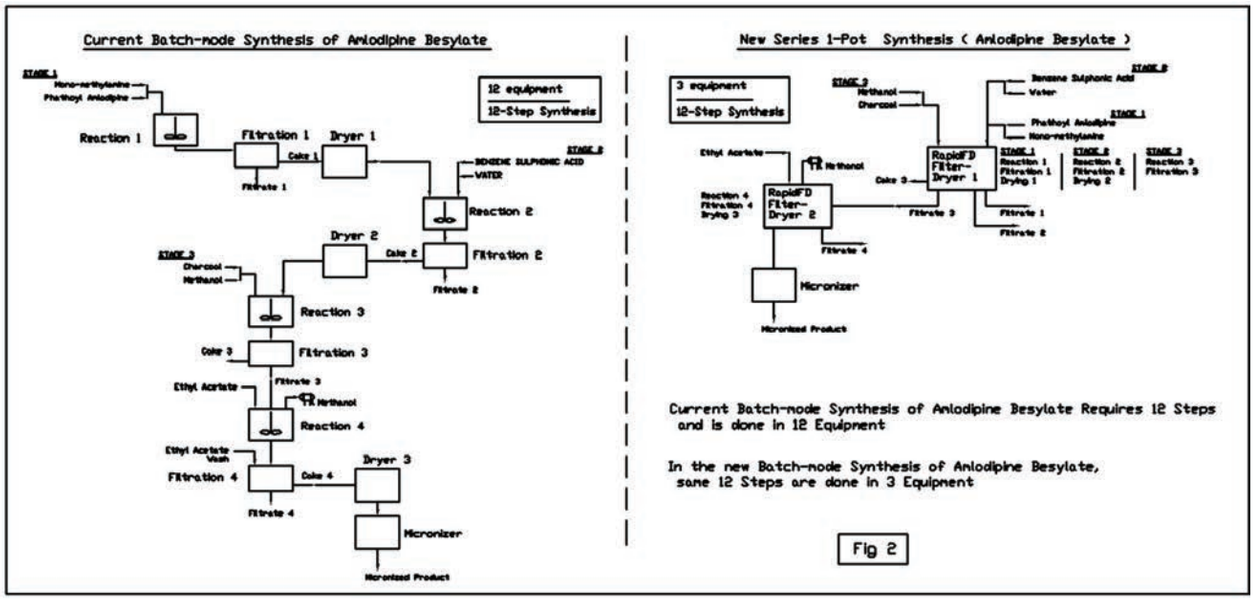


Fig. 2

"Table 1 : Benefit from adoption of One-Pot Synthesis Technology (Ref-3) (In Setting up of New Plant to manufacture APIs / Bulk Drugs & Intermediates)"		
	Conventional Batch-mode	New One-Pot Batch-mode
Land 14000 sq. ft.	Rs. 46.0 Lacs	Rs. 46.0 Lacs
Building	Rs. 90.0 Lacs	Rs. 90.0 Lacs
Plant & Machinery	Rs. 365.0 Lacs	Rs. 300.0 Lacs
Total Cost	Rs. 5.01 Crores	Rs. 4.36 Crores
Production Capacity	280 kgs/day or 8.5 Mts/month	500 kgs/day or 15 Mts/month
Operating Manpower	60	45
Mean Utilization	65%	80%

- Higher yield.
- Substantial reduction in process / synthesis cycle time (15% to 60% of current cycle time).
- Elimination of some steps in the manufacture of APIs / Drugs / Intermediates.
- Lower energy costs.
- Reduction in Material handling.
- Reduction in space for manufacture of a product.
- Reduction in manpower required in the synthesis.
- Possible elimination of use of solvent in some stages of synthesis
- Overall equipment cleaning times greatly reduced compared to current practice.
- Improvement in the bottom-line of the Company.
- Lower Investment outlay for a given capacity Plant, compared to Investment in current practice.

To give a sense of the benefit this One-Pot batch-mode Synthesis offers, consider the setting up of a small-to-medium scale Bulk Drug / API manufacturing unit for synthesis of 12 products and their intermediates. A Company, adopting the conventional batch-mode synthesis route, made an estimate of Investment in Land, Building and Machinery which is given below under 'Conventional Batch-mode' column (column 2). To produce same batch-sizes of the 12 same products and intermediates considered in the original project, an estimate of Investment on facilities based on the new One-Pot synthesis described above is listed in column 3, for comparison. The Production-capacity of such a project based on the new One-Pot Synthesis is also given below.

It can be seen that the new One-Pot-Synthesis-based Investment would not only be lesser by Rs 65 Lacs but would also mean a higher Production capacity of plant since the batch-cycle times would be lesser. Lesser Operating Manpower would be required and, since lesser equipment would be needed, lesser cleaning times would result leading to higher productive utilization of equipment.

The example considered was of a small-to-medium scale plant. The benefits would be significantly larger for larger capacity Investments. The plant size as also the building size would be significantly smaller, translating into lesser Investment value.

The new route to batch-mode processing, One-Pot Synthesis, justifies the continuance of use of batch-mode synthesis in the years ahead, taking the sheen off the Continuous-mode Synthesis. The Continuous-mode Synthesis would no longer offer same advantages as claimed today over the Batch-mode. It would therefore do the Chemical and Allied Industries a whole lot of good to quickly upgrade their batch-mode technology and incorporate more of One-Pot synthesis into their existing production stream (while also considering new Plants on the basis of One-Pot Processing) and reap the benefits of continuous-mode synthesis ■

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