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2020 Reflections:
Global Biopharma Leaps Ahead Despite Challenges

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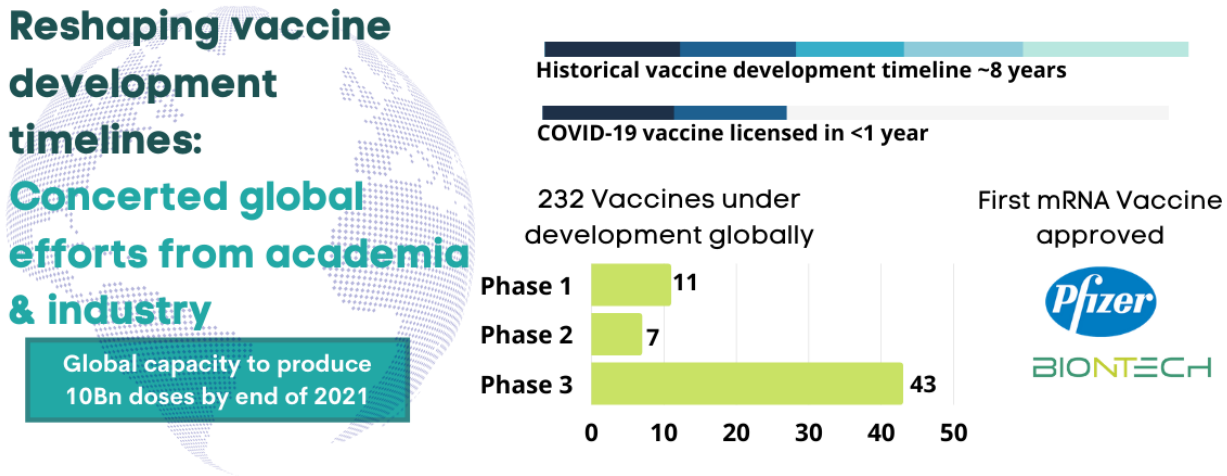
December 2020

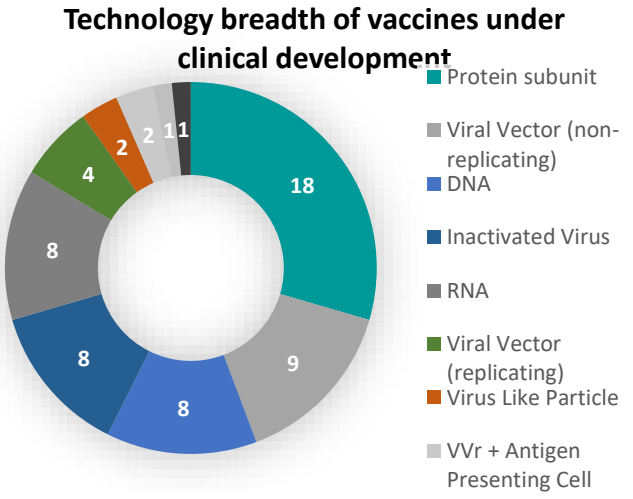
2020 has been a challenging year. However, it is also the year where the power of scientific triumph is emphatic in the re-scripted vaccine development timelines. There was a spotlight on patient convenience and regulators & industry jointly accelerated access to formulation innovation. Biosimilars and clinical development programs took a setback. But finally, there was much overdue policymaker focus on nurturing pharma manufacturing resilience and bridge voids in the country level value chain engagement.

COVID-19 vaccines: Global collaborations & concerted scientific effort sets record benchmark for pace of development

The COVID-19 pandemic and consequent economic and public health impact ravaged most of the year gone by. The silver lining is the spirit of collaboration and the power of science that has underlined the global quest for a solution. Pace of development of the COVID-19 vaccine will go down in history as a new benchmark.



By March 2020, the month when WHO declared COVID-19 as a pandemic, 30 vaccine candidates were already under development globally and two (Moderna and CanSino) had already commenced Phase I clinical trials (Sathguru's March 2020 roundup). At every milestone in the vaccine development journey new benchmarks have been set; and resolute efforts from early 2020 were critical for scripting the current record. This gets emphatic when seen against the context of SARS epidemic in 2003 when it took almost three months just to get the viral genome sequenced.



We now stand on a formidable pipeline of 232 vaccines with 60 in clinical development. Creating history, several countries across the world have commenced vaccination for COVID-19 within nine months of it being declared a pandemic. The USFDA has approved Moderna and Pfizer-BioNTech vaccines,

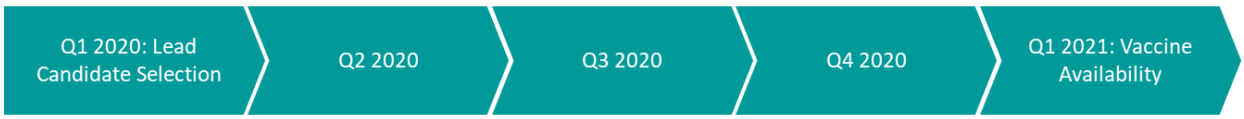
MHRA has approved Pfizer-BioNTech and AstraZeneca-Oxford vaccines, Russia has approved the Sputnik V, EMA has approved the Pfizer-BioNTech vaccine and China added to the list after approving Sinopharm's vaccine couple of days before the year end. While global access remains a puzzle not fully addressed, the geographic spread of the Phase III pipeline is a great source of hope. We step into 2021 with great possibility of delivering to the world about 10 billion doses of the COVID vaccine from companies across geographic borders.

The journey has not been bereft of its fair share of setbacks and challenges. It was also a reminder of the reality of technology risk that is inherent in biopharmaceutical product development and translational research. Delays set back two fore-runners Inovio and Novavax that could have otherwise crossed the Phase 3 line by end of 2020. Clinical data disappointments impacted the Sanofi-GSK adjuvaneted vaccine, the University of Queensland-CSL program was halted due to potential interference with HIV screening and about a dozen other undeclared setbacks are folded into the preclinical long tail. And a big unknown looms on the world as 2021 dawns, the potential for efficacy against the mutated strain that emerged in UK and South Africa but now reported in several other countries including US and India.

Despite the setbacks, the global quest for COVID-19 vaccine is historic and will be remembered as a major scientific triumph. It has been no mean task to recalibrate the historical 8 to 10 year journey to under a year. And that too, while nurturing the technology breadth embodied in the global pipeline and ushering in the first ever mRNA vaccines (and potentially) the first DNA vaccines to get approved.

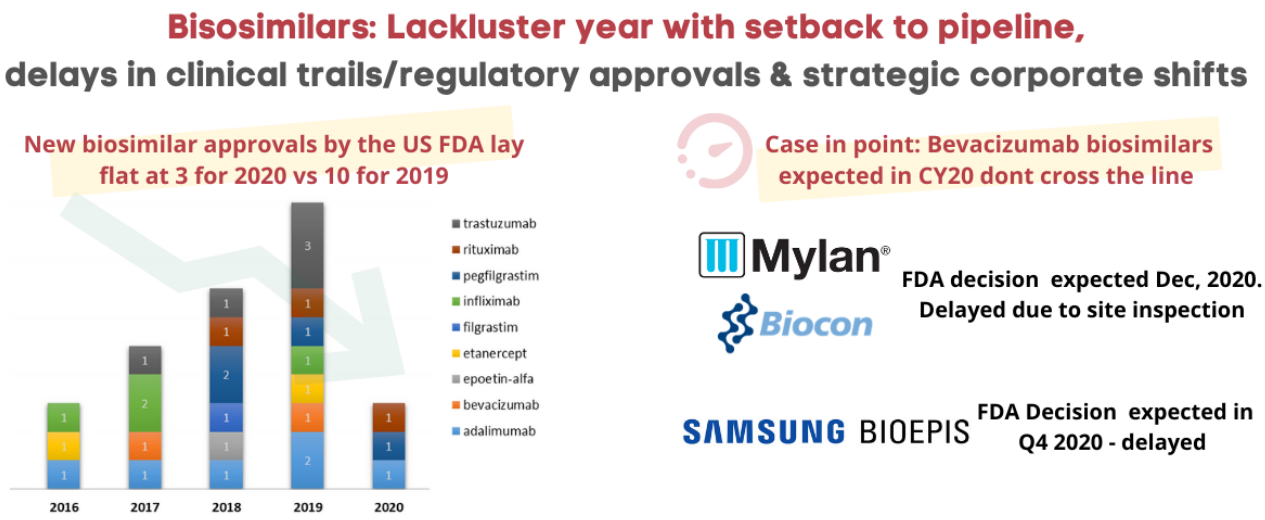
Typical Vaccine Development Timeline: Indicative

COVID-19 Vaccine Development Timeline: Indicative

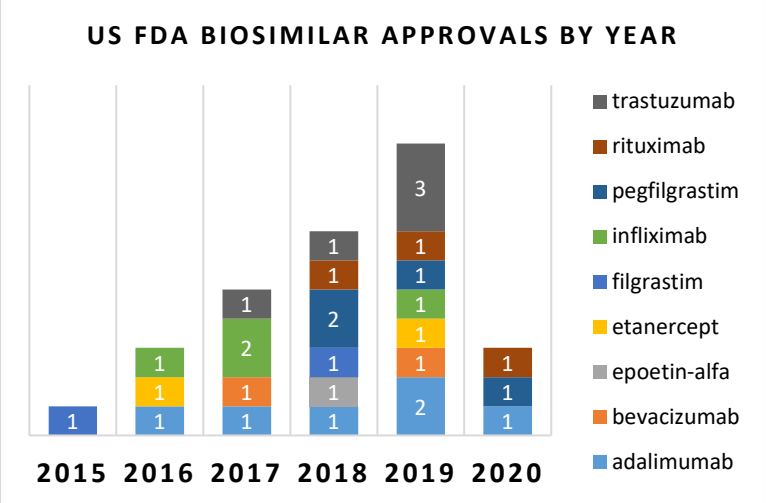


Vaccine Developers	Q1 2020	Q2 2020	Q3 2020	Q4 2020	2021
Moderna/Lonza	Phase I	Phase I	Phase II/III	Phase III, EUA approval	**Vaccine available**
Oxford/AstraZeneca	----	Phase I, Phase II/III	Phase III	Phase III interim results	**Vaccine available**
Pfizer/BioNTech	----	Phase I, Phase II	Phase II/III	Phase III, EUA approval	**Vaccine available**
Gamaleya/Sputnik	----	Phase I	Phase II/III	Phase III interim results	**Vaccine available**

Lackluster year for biosimilars – marked by regulatory and development delays



While the COVID-19 vaccine itself has created new benchmarks for pace of biotech product development, the pandemic otherwise resulted in major setbacks for clinical trials across the world. Data reported from across countries pointed to clinical trial enrolments recovering the steep 70% drop in April and moderating to about a 30% drop by Q2 and Q3 2020. Invariably, this implied delays in intended product development plans. Regulatory activity was concentrated on COVID-19 related measures and operational challenges of a global pandemic resulted in regulatory delays further affecting the biopharma industry. Restricted travels slowed down regulatory evaluations, manufacturing site inspections and thereby product approval decisions.

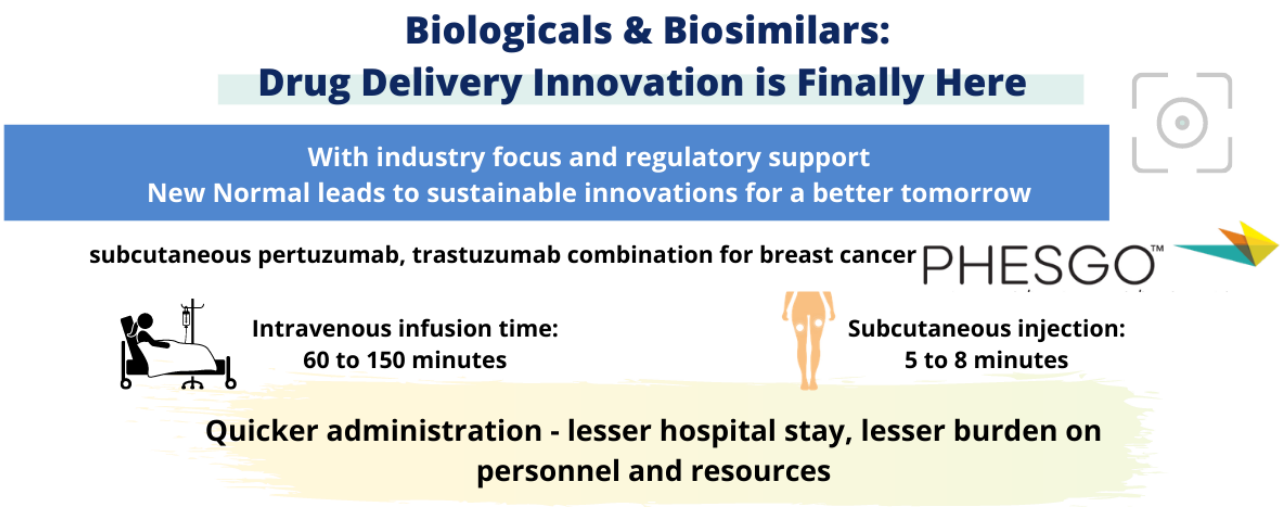


Biosimilars were no exception. The lack luster year was marked by delays, substantially fewer approvals and no major reason for cheer. New biosimilar approvals by the US FDA stooped to a low of 3 approvals during 2020 from the remarkable level of 10 approvals in 2019. The delay was caused by several factors – practical challenges of enrolling and running clinical trials in the new normal of 2020, regulatory actions hindered and some dampening of corporate investment appetite due to an overall focus on cash conservation.

While some bevacizumab biosimilars faced hurdles due to regulatory delays, Centus Biotherapeutics faced a setback due to the lawsuit filed by Genentech alleging patent infringement on the molecule. While the primary patents on the originator reference molecule bevacizumab have expired in 2019, multiple secondary patents active in USA continue to guard the formulation and manufacturing process and platform. The biosimilar is still under review by the FDA and any patent litigation would substantially delay the launch of the biosimilar. We have covered this news in detail in our November Newsletter. Genentech witnessed a sales erosion of approximately USD 900 million in the first nine months of 2020 and two marketed biosimilars currently – Mvasi and Zirabev have acquired a 40% share in the US market. On account of this, Avastin's parent continues to stall future biosimilar competition and sales erosion through the infamous legal route.

The overall setback in the biosimilars segment is a cause of concern. This could impact anticipated timeline of launches and affordable access to critical biological drugs. We embark on 2021 with hope that catchup efforts will propel the pipeline forward and 2021 will be significant for industry, patients and healthcare systems across the world.

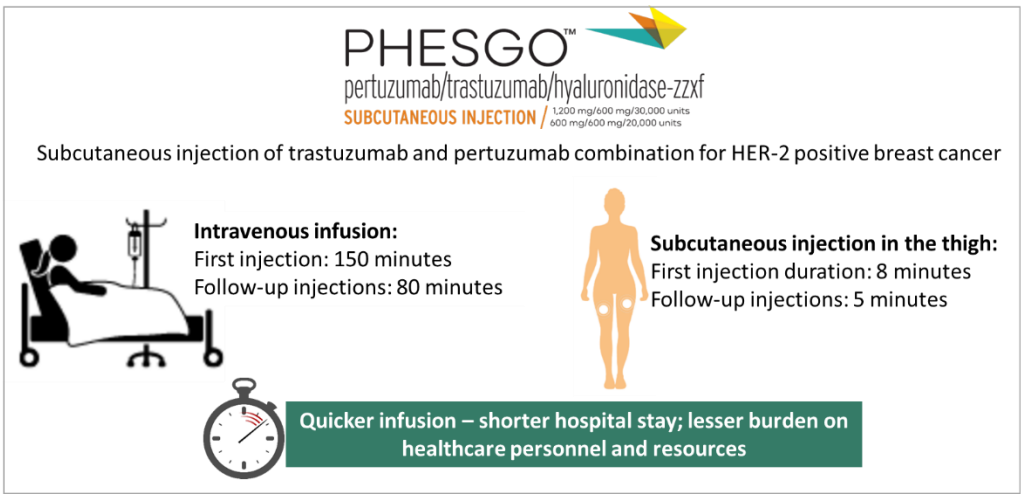
Patient friendly drug delivery – Adapting to the new normal & sustainable impact



Healthcare delivery ecosystems across the world were the hallmark of resilience all through 2020. Delivering care in the new normal called for all stakeholders to adapt. Especially so, in the case of chronic care, emergency care and care for immunocompromised patients. As we wade out of the woods, we are excited about the sustainable impact of innovations that the new normal accelerated.

Patient convenience was at the heart of drug delivery innovation that COVID-19 catalyzed. The last nine months witnessed accelerated development effort and approval of several oncology drug formulations that can be administered with substantially shorter infusion times reducing length of hospital stay or can be administered at home.

An indicative example is Genentech's July 2020 FDA approval for Phesgo™ , a subcutaneous injection of trastuzumab and pertuzumab that can be delivered in less than 8 minutes as compared to the conventional 80 minutes intravenous infusion. While the move also represents lifecycle management to ringfence from

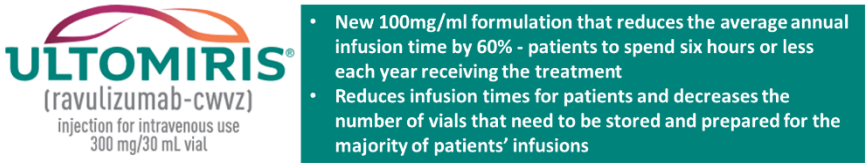


biosimilar competition, patient convenience and health-economic benefits are here to stay as drivers of formulation innovation. We have covered about it in detail in our PharmForward post here.

Celltrion, a company with a focus on bio-betters as a strategy for a competitive branding, received EMA nod for its subcutaneous infliximab biosimilar – the first in the world – making a remarkable improvement over the current intravenous infusion formulation to provide patients more control and flexibility over their treatments for various auto-immune conditions.

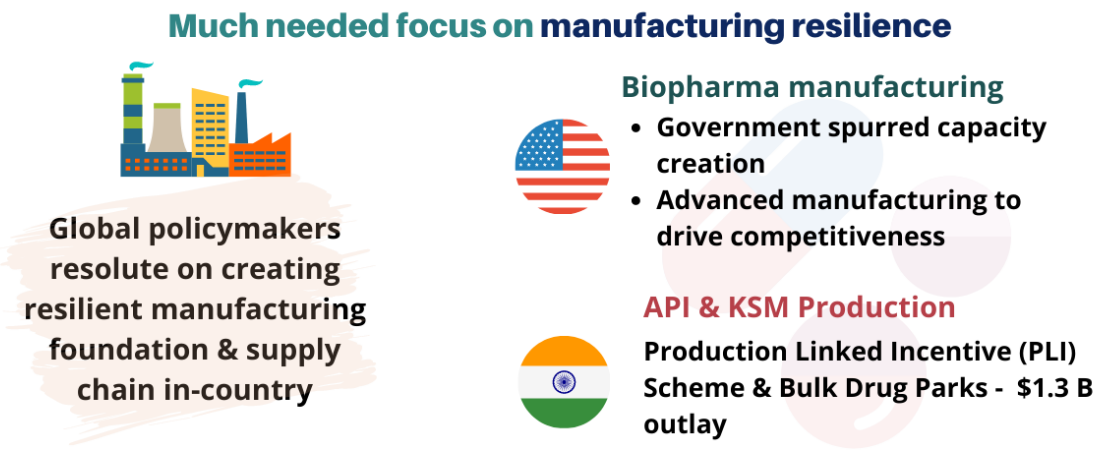
These innovations and improvements in formulation was not limited to biosimilas as two biologics – Kesimpta (ofatumumab) and Ocrevus (ocrelizumab) were introduced in a self-administered and quicker infusion versions respectively for Multiple Sclerosis. Both drugs target B-cells and bind with them to prevent auto-immune mediated damage on the nerve cells.

In October 2020, Alexion was granted approval for a new version of its block-buster drug Ultomiris for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). This new version has a shorter infusion time – 60% lesser than the existing 10mg/ml version. This is particularly pertinent in the current COVID-19 context where hospitals are already stretched to capacities, patients would be hesitant for longer hospital stays and therefore the quicker acting versions of critical drugs would be highly welcome.



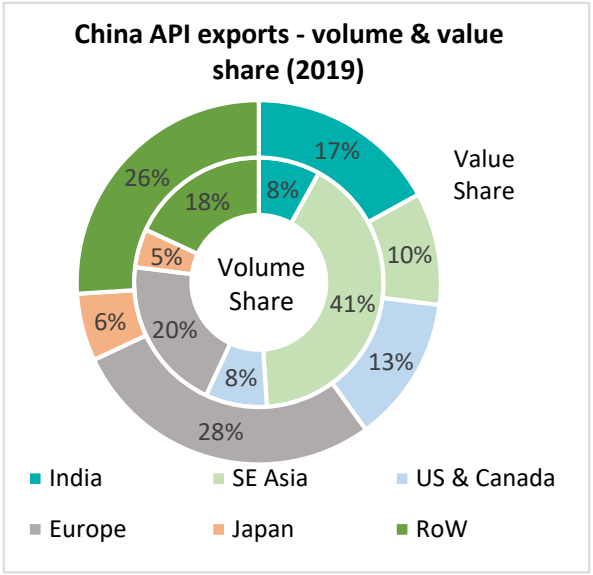
While the catalyst COVID-19 will be behind us, the sustainable impact of this trend will be far reaching. We are highly encouraged by the propelling forces for this momentum around delivery innovation and patient centricity – these are telling examples of the power of stakeholder collaboration. While industry has responded with agility and sustained investments, regulatory impetus and support has provided the tailwinds. We kick off 2021 on this formidable foundation of innovation momentum. Spotlight: Patient centricity – in 2021 and beyond.

Finally, long overdue focus on manufacturing resilience across geographic borders



The COVID-19 pandemic severely disrupted manufacturing operations across the globe. Beyond manufacturing, global supply chains were set astray and the risk of import dependence was starkly evident.

Over the last several decades, pharmaceutical value chain, especially for generic drugs, has become more geographically concentrated in a smaller set of countries globally. While China has emerged as a major base for API production, India has emerged as the dominant hub for high quality formulation manufacturing. Analysis of the composition of China's ~ $30billion API export points to pervasive global dependence on Chinese starting material for the pharmaceutical value chain. This has led of shrinking of domestic manufacturing capacity in most countries across the world, especially for generic drugs. In countries where historical capacity was lean, there has been a progressive deterioration of business case for new manufacturing investments in generics. Constant pricing pressure in generic drugs across geographic markets (including the US) and quest for cost competiveness has deterred industry investments and driven deeper import dependence. Hence, for most essential drugs that are now highly genericized, formulations are often imported. Even if formulations are produced domestically, the API are imported. Domestic API production is also often a façade with high import dependence for the building blocks, intermediates and key starting materials (KSMs).

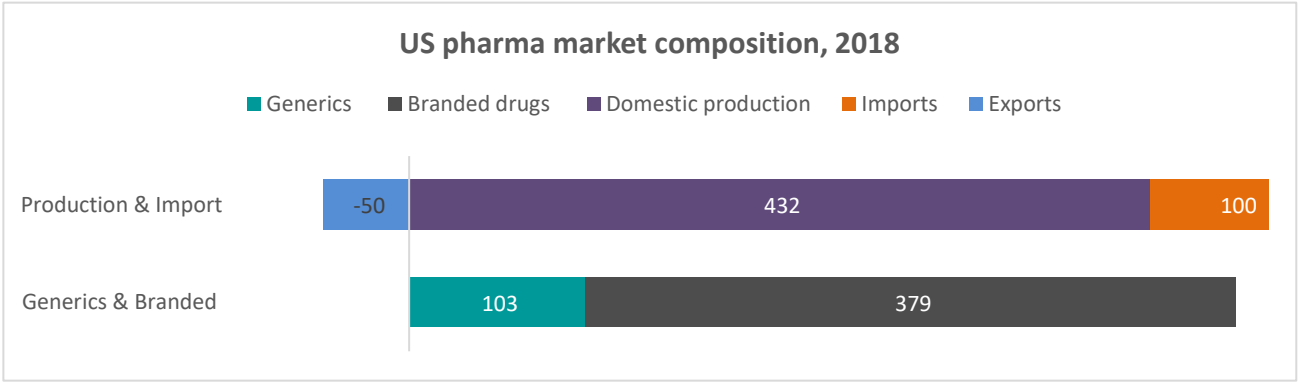


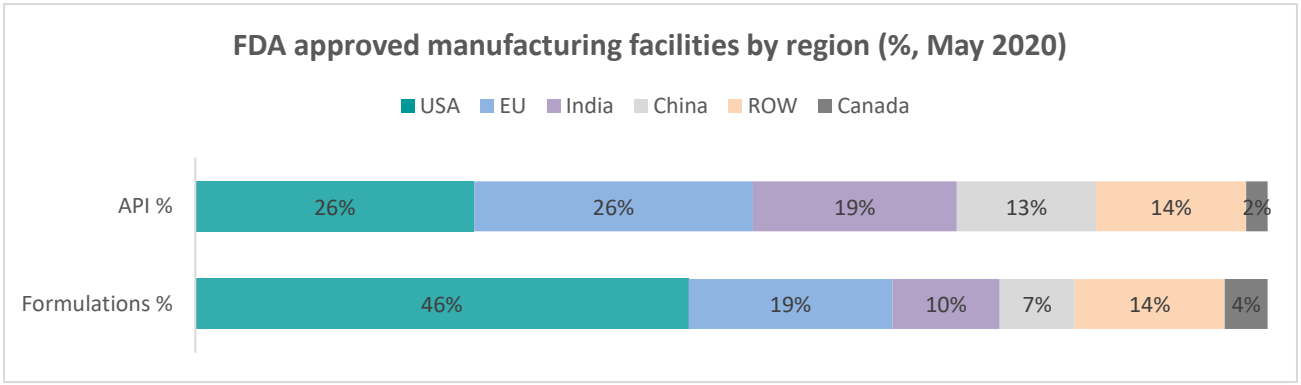
COVID19 led disruptions have laid bare the gaps in the pharma manufacturing value chain at the country level. This has triggered long overdue action from policymakers to nurture more resilient manufacturing engagement in country for essential drugs. The awakening spanned high and low/middle income countries, the east and the west:

United States – Catalyzing domestic productions & advanced manufacturing for competitiveness

The US continues to be the largest pharma market in the world, clocking close to $450billion. Import dependence is limited to about $100billion; and value wise ~60% of the imports are from Europe and UK primarily for branded drugs. However, the challenge to the ecosystem resilience is from the high import dependence for generics, especially essential drugs such as anti-infectives. As of 2018 end, while generics only comprised 21% of the pharma market by value, they had breached 90% of number of prescriptions dispensed.

Attention to the issue of pharma resilience has snowballed in many ways: a Congressional hearing in October 2020 with the Director of CDER, FDA testifying with data on number of facilities outside the country, implications for national security and measures to revitalize domestic pharmaceutical manufacturing. The testimony acknowledges the growing dependence on imported Chinese API (with 72% of approved API facilities being overseas), dearth of data on quantum of dependence and proposes advanced manufacturing to foster competitiveness in American companies who will also be supported by extra-mural and intra-mural grants.





The US Government's focus was also evident in multiple instances of stimulative funding to industry to create domestic production that can negate offshoring. Indicative examples include:

$765million to Kodak: Initiated as a domestic response to COVID-19, under the Defense Production Act (DPA), Eastman Kodak Company (Kodak) received a USD 765 Million loan from US International Development Finance Corporation (DFC) to launch Kodak Pharmaceuticals. The loan will accelerate repurposing and expanding the facilities in Rochester, New York and St. Paul by incorporating manufacturing and advanced technology

capabilities. When fully operational, Kodak Pharmaceutical will have the capacity to produce about 25% of the APIs used in non-biologic, non-antibacterial, generic pharmaceuticals.

$354million to Phlow Corporation led consortium: One of the largest ever grant awards by BARDA, the 4-year and $354million contract with BARDA (extendable to $812 million over 10 years) will support creation of a new drug manufacturing facility in Virginia along with increased capacity to produce active pharmaceutical ingredients (APIs) and chemical compounds for those ingredients. Ampac Fine Chemicals, a custom API manufacturer; Civica RX, a non-profit generic drug company; and the Medicines for All Institute at Virginia Commonwealth University's College of Engineering

$285million to Paratek: BARDA also extended $285million to Paratek Pharmaceuticals, maker of novel antibiotic Nuzyra for on-shoring of the manufacturing supply chain. Though commitment for stock piling of Paratek's drug is only for 10,000 courses of treatment, BARDA's support will negate future dependence on the all-European base of API and formulation that Paratek currently relies on.

India – Reducing API import dependence and fostering value chain resilience

Shrinking of API manufacturing base has been true even for countries such as India. India has rightfully earned the reputation of ''Pharmacy of the World" and exported pharmaceutical products worth $15.61billion in 2020. However, India pharma manufacturing landscape represents stark contrasts. Leading export oriented pharma companies thrive on backward integration (~ 70% in larger companies) to power competitiveness in global generics. But, at the other end, several smaller API companies holding 1 to 5 DMFs and revenue less than $100 Million have faced mortality. Lack of competitiveness vs lower priced Chinese APIs continues to deepen import dependence for several essential drugs. Even in products where API import dependence is relatively lower, the health system and supply chain continue to be fragile if there is high import dependence for intermediates and key starting materials (KSMs). Policy action was long overdue and the 2015 Katoch Committee Report emphatically called for action. India's policy stimulus has included two pronged approach covering 53 APIs identified as essential drugs with high import dependence:

Production Linked Incentive (PLI) Scheme

Scheme structure: 5% to 20% financial incentive on sales for 6 years

Target Segment	Threshold Investment	Quantum of Incentives
Fermentation based KSM/DI	$ 53 M	FY 2023 – 24 to FY 2026 – 27: 20% FY 2027 – 28: 15% FY 2028 – 29: 5%
Fermentation based niche KSMs/DI/APIs	$ 7 M	
Key Chemical Synthesis based KSMs/DIs	$ 7 M	FY 2022 – 23 to FY 2027 – 28: 10%
Other Chemical Synthesis based KSMs/DI/APIs	$ 3 M	

Indicative Drugs covered

- **Fermentation based KSMs/DIs**: Penicillin, Erythromycin Thiocynate, Clavulanic acid,
- **Fermentation based niche KSMs/DIs/APIs**: Neomycin, Gentamycin, Vitamin B1, etc.
- **Key chemical synthesis based KSMs/DIs**: Cyclohexane Diacetic Acid dicyandiamide(DCDA), para amino phenol
- **Chemical synthesis based KSMs/DIs/APIs**: Meropenem, atorvastatin, olmesartan, no minimum annual production capacity mentioned for ritonavir, lopinavir

Overall program outlay: $920Million

Bulk Drug Parks

- Creation of 3 bulk drug parks in the country
- Funding for 70% to 90% of common cost for infrastructure
- Grant of upto ~$140 Million for each bulk drug park
- Duration of the Scheme is from FY 2020-202 1 to FY 2024-2025

Overall program outlay: $400Million

Production Linked Incentive Scheme: In a bid to counter the persistent business threat of low priced Chinese imports, the Government has introduced the Production Linked Incentive Scheme (PLI) for domestic manufacture of 53 APIs where import dependence is a threat to access to essential drugs as well as certain Key Starting Material (KSMs) and Drug Intermediates (Dis). With an overall outlay of $920Million, the scheme hopes to provide production linked incentives of 5% to 20% on revenue for the stipulated drugs.

Bulk Drug Parks: Capex recovery for new API investments is a deterred due to marginal cost based imports from Chinese companies. As part of the efforts to create competitiveness for Indian companies, the Government has committed to fund 70% to 90% of the costs of common infrastructure in bulk drug parks that will provide soft landing for API companies. This will enable environmental compliance in production without burdening companies with capex for common Effluent Treatment Plants.

***Our 2020 initiative**: In our quest to bring you timely and critical insights from across the global biopharma spectrum, in 2020 we beta launched PharmForward, a Sathguru initiative that is the first of several steps in a more comprehensive suite of competitive intelligence solutions planned. Follow us and join the journey: https://www.sathguru.com/pharmforward/*