Scrip Asia 100

Pharma Intelligence

Foreword

While much of Asia has started gradually returning to some form of post-pandemic normalcy over the past year, at the time of writing China still had shown no signs of loosening its rigorous "COVID Zero" policies. Mass testing, strict local lockdowns and the virtual closure of its international borders appear set to continue well into 2023.

COVID-19 has become an engrained feature of everyday life and close to three years after the Wuhan outbreak some things remain the same and others have changed – perhaps the single biggest difference has been a strategic shift in many countries to various attempts to "live with the virus."

The afterglow of the pharma industry's central global role in combating SARS-CoV-2 with vaccines and drugs is also gradually fading – along with emergency government funding - but the multiple changes and challenges wrought by the pandemic on the industry roll on.

Supply chain disruptions, moves to repatriate manufacturing and wider adoption of remote and digital tools in product development and commercialization are just some of the results still playing out, which in many cases look set to become more permanently embedded in standard practices.

Meanwhile, equitable access to what looks likely to be a steady procession of follow-on vaccines targeting dominant variants remains a key issue globally, one moving into the spotlight again around the monkey-pox outbreaks.

Besides the ongoing pandemic response and impact, the APAC biopharma industry has been pursuing business as usual. While there have been no landmark M&A deals over the past year, China has continued to emerge as a hotbed of rising innovation, with mRNA becoming the trending new area alongside the increasingly crowded immuno-oncology space.

Alongside the country's independent push into global markets – albeit with some major road bumps in the US – its R&D capabilities are also being increasingly tapped by western big pharma, although cooling investor sentiment may mean a more inward-looking deal-making environment.

Elsewhere, India continues to progress its vaccines sector across multiple fronts, while its generic firms face rising pricing pressures in the US. South Korea moves steadily down the path to more innovation and globalization, and while it has long been a mature market, Japan remains a key part of the regional picture, making moves to support homegrown vaccines and drugs for future pandemics.

As always, we hope the carefully curated selection of data, insights and analysis in this year's Scrip Asia 100, which includes content from across our on-the-ground team, will help you make sense of this large, diverse and complex part of the pharma world.

Ian Haydock
Editor-in-Chief, APAC
Citeline

Scrip Asia 100
Pharma Intelligence

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Scrip is published by Informa UK Limited.

ISSN 0143 7690

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Real-World Experience Driving Continuous Improvement In Decentralized Clinical Trials

Asia Pacific continues to be an attractive location for clinical trials given the large population, diverse ethnicities, treatment naïve population and rapid growth of the pharmaceutical market. At the same time the region's consumers and industry leaders have always been recognized for their openness and acceptance of new technologies, therefore it seems likely that the shift to decentralized clinical trials will be smooth. However different the regulation, cultures and languages may be between Asia Pacific and the rest of the world, attracting, recruiting and retaining patients continue to be universal challenges. So how can sponsors, regardless of the location of the trial, ensure that they reap the recognized benefits of decentralized clinical trials, increasing patient recruitment, retention and compliance?

The deployment of decentralized clinical trials over the past few years has generated valuable real-world experience to drive continuous improvement in the virtual setting. Trial sponsors now have a clearer view of critical success factors such as early planning to ensure optimal engagement with patients and sites, selecting the right home-care services, wearables or sensors.

Getting the essentials right can be transformative, as illustrated by CHIEF-HF, a decentralized study of canagliflozin in heart failure. It achieved around 98% protocol compliance, using electronic patient-reported outcomes (ePRO) and eDiary technologies. Feedback from patients was highly encouraging. "Patients would recommend participation to friends and family, they found the devices easy to use and the reminders helpful," notes Kim Hedges, ICON's senior clinical program director.

Patient satisfaction is a significant driver of patient compliance in clinical trials. The CHIEF study emphasized the value of real-time support during the trial via virtual concierge services. These services helped with welcoming patients, managing consent, scheduling visits, responding to patient concerns, collecting reported events or retrieving equipment.

CUSTOMIZED TRAINING FOR SITES AND PATIENTS A CORNERSTONE FOR SUCCESS

Growing experience with decentralized trials has also highlighted some continuing challenges. One of these is the importance of site training. "Often there may be gaps between the site-initiation visit and other processes leading up to the first patient in. Some retraining may be needed to refresh sites on the responsibilities set out in trial documentation and accompanying materials." Comments Hedges.

Sponsors must also be careful not to lose sight of patients in the home setting. By increasing touchpoints with trial participants, sponsors can ensure patients are filling out their eDiarys or generating ePROs on a scheduled basis. With a central team monitoring these inputs digitally behind the scenes, sponsors can identify and address any compliance issues sooner rather than later.

Early training of patients is part of the sponsor's roadmap for success in decentralized trials. "We actually have a team that runs through that end-to-end experience, for sites and patients," Hedges points out. "If we're going to give patients an application and connected devices to use, we want to make sure that's a positive experience for them."

Trial apps incorporating documentation and videos facilitate onboarding, so that patients have a reference point to help keep them on track. "If we've done our job right, they can use the application, go through their eDiary and ePRO, with minimal disruption to their normal daily schedule" Hedges comments.

Sponsors may also face varying degrees of participant familiarity with digital devices and media. "We can't assume that all sites and patients have the same level of comfort with decentralized processes," Hedges comments. "Even participants with experience of smartphones or apps may struggle during a trial if they are dealing with other issues in the home setting."

DEVICE AND SERVICE OPTIONS

Selecting the right devices for a decentralized trial is also far from straightforward. The sheer range of possibilities "can be overwhelming", Hedges acknowledges. ICON has a team dedicated to ensuring, for example, that selected devices tick boxes such as operational excellence, safety and patient engagement. Study objectives will feed into these considerations.

Device selection also depends on the therapeutic area involved, study duration, endpoints, patient-burden assessments, whether the trial is blinded or not, and whether it involves passive monitoring or active assessment. Patient-centricity and device useability are paramount, as are device characteristics such as battery life and connectivity. Sponsors also need to think about device validation, data transfer, storage and visualization, and regulatory issues such as privacy and security.

"We go through a pretty rigorous process of vetting the devices," Hedges says. That includes considering what type of device best suits the patient's daily routine: whether they wear a watch or armband, for example; or whether the device and any associated apps include remote capability for data transmission. ICON uses patient and clinician user groups to test out the practicalities of new wearables or other devices. That might be something as simple, yet key to compliance, as how easy it is to place a blood pressure cuff correctly to capture and transmit accurate readings on the device.

Selection of other virtual care options, such as in-home nurse services, is also closely managed. For each trial, a dedicated team at ICON, traces the whole patient journey through the trial and makes recommendations on service elements, based on therapeutic expertise and parameters such as study outcomes.

It is crucial that the whole infrastructure to support patients and sites is in place before decentralized trials go live and that this is maintained throughout the trial.

Reducing the administrative burden on sites, such as determining whether patients want to participate and explaining how the trial works, is another important driver for early planning and action. Once the study is up and running, the sheer volume of data points can be another challenge for sites. Using a dashboard enables sites to sift out "the data they need", Hedges says. "It doesn't take a phone call to gather and assess that information, because the information is displayed right in front of them."

DEFINING ROLES AND COMMUNICATION CHANNELS TO BUILD STAKEHOLDER CONFIDENCE

Defining and clarifying roles and responsibilities clearly in advance gives sites and physicians confidence that the team has experience in overseeing patients virtually, and that any issues arising from interactions between, for example, patients and concierge services, will be escalated and conveyed promptly to sites.

Seamless connectivity and communications between study teams and sites help to keep decentralized clinical trials moving forward on time and target. ICON uses a number of established mechanisms, such as shared sites or integrated systems, to enhance interaction between teams and sites, as well as looking to newer technologies like chatbots. Messages can be exchanged between the trial platform and dashboard, or with trial patients through the same channel.

CLOSER TO THE POINT OF CARE

Once physicians understand that the technology driving decentralized trials is complementary, and not about increasing burden or affecting their relationship with the patient, they are more comfortable managing patients outside traditional brick-and-mortar settings.

By streamlining interactions with, and enhancing confidence and trust in, health care systems through enhanced information flow and patient-centric strategies, decentralized trials can also improve patient engagement with care processes as they shift responsibility to self-management of conditions in the home.

This is especially pertinent as sponsors seek to replicate real-world conditions in technology-enabled studies. "We know that, ultimately, the majority of patients want to be outside the clinic and hospital setting," Hedges says. "They want to be at home. That is where they manage chronic diseases, and have done for years."

In that sense, decentralized clinical trials conducted remotely can actually bring patients closer to the point of care. As Hedges points out: "The more we can align with what feels more natural for a patient, which is being at home and taking care of as many of their health issues as possible at home, with the right support, that is a win-win for patients as well as trial sites and sponsors."

SCRIP ASIA 100: 2021 PHARMACEUTICAL SALES

RANK	COMPANY	2021 PHARMA SALES ($M)	CHANGE FROM 2020 (% BASIS)
1	Takeda	32514	9%
2	Sinovac Biotech Ltd.	19375	3694%
3	Astellas	11808	4%
4	CSL	9980	9%
5	Otsuka Pharmaceutical	8905	0%
6	Eisai	6889	14%
7	Sun Pharmaceutical	5199	15%
8	Sumitomo Dainippon Pharma	4700	-3%
9	Shanghai Fosun Pharmaceutical Group	4461	41%
10	Daiichi Sankyo	4456	-51%
11	Sino Biopharmaceutical	4165	21%
12	Jiangsu Hengrui Medicine Co. Ltd.	4016	0%
13	Shanghai Pharmaceutical Group Co., Ltd.	3891	13%
14	Asahi Kasei Pharma	3789	-1%
15	Mitsubishi Tanabe Pharma	3516	-1%
16	CSPC Pharmaceutical Group Ltd.	3250	3%
17	Kyowa Hakko Kirin	3209	8%
18	Aurobindo	3173	2%
19	Cipla	2939	15%
20	Sichuan Kelun Pharmaceutical	2679	12%
21	Dr Reddy's	2567	0%
22	Shionogi	2510	9%
23	Joincare Pharmaceutical Group Industry Co., Ltd.	2466	26%
24	Shandong Buchang Pharmaceuticals Co., Ltd.	2444	5%
25	Santen	2274	3%
26	Ono	2241	11%
27	Lupin	2191	7%
28	Zydus Lifesciences (earlier Cadila Healthcare)	2043	0%
29	Harbin Pharmaceutical Group Co., Ltd.	1985	27%
30	Livzon Pharmaceutical Group	1870	23%
31	Sawai	1766	1%
32	Meiji Holdings	1712	-6%
33	Teijin Pharma	1672	20%
34	Celltrion	1671	6%
35	Glenmark Pharmaceuticals	1665	13%
36	Nichi-Iko	1631	-7%
37	Shijiazhuang Yiling Pharmaceutical Co.,Ltd	1569	23%
38	Jiangsu Hansoh Pharmaceutical	1540	22%
39	Yuhan Corp	1475	7%
40	Zhejiang Medicine Co., Ltd.	1415	33%
41	CR Double-Crane Pharmaceuticals Co., Ltd	1413	15%
42	Towa	1411	-3%
43	Samsung BioLogics	1371	39%
44	GC Pharma	1344	5%
45	KPC Pharmaceutical Inc.	1280	14%
46	Chong Kun Dang	1174	6%
47	Kwang-Dong Pharmaceutical	1170	11%
48	Torrent Pharmaceuticals	1139	5%
49	Biocon	1107	15%
50	Nippon Shinyaku	1099	3%

SCRIP ASIA 100

SCRIP ASIA 100: 2021 PHARMACEUTICAL SALES

RANK	COMPANY	2021 PHARMA SALES ($M)	CHANGE FROM 2020 (% BASIS)
51	Hisamitsu	1095	2%
52	Hanmi Pharm	1052	15%
53	Zhejiang Huahai Pharmaceutical Co., Ltd.	1030	10%
54	Daewoong Pharmaceutical	1008	12%
55	Shenzhen Hepalink Pharmaceutical Group Co., Ltd.	987	28%
56	3SBio	972	21%
57	Luye Pharma Group Ltd.	972	21%
58	Kyorin	961	0%
59	Zhejiang Conba Pharmaceutical Co., Ltd.	954	11%
60	Mochida	938	-2%
61	Piramal Healthcare	907	16%
62	PT Kimia Farma	900	30%
63	Jubilant Pharmova (earlier Jubilant Life Sciences)	829	0%
64	SK Bioscience	812	0%
65	Maruho	799	-4%
66	Dong-A Socio Holdings	771	16%
67	Shandong Lukang Pharmaceutical Co., Ltd.	758	24%
68	Japan Tobacco	732	-1%
69	Alembic	718	-1%
70	CK Life Sciences	695	92%
71	Kaken	693	11%
72	SSY Group Limited	689	25%
73	Hualan Biological Engineering, Inc.	688	-6%
74	HK inno. N (formerly CJ Healthcare)	673	32%
75	Laurus Labs Ltd.	668	10%
76	Shanghai RAAS Blood Products Co., Ltd.	665	66%
77	Jeil Pharmaceutical	661	13%
78	Shanghai Junshi Biosciences Co., Ltd.	624	170%
79	Innovent Bio	620	81%
80	Takara Bio Inc.	617	43%
81	Jiangsu NHWA Pharmaceutical Co., Ltd.	610	25%
82	Zhuzhou Qianjin Pharmaceutical Co., Ltd.	568	8%
83	Jiangsu Kanion Pharmaceutical Co Ltd	566	29%
84	Walvax Biotechnology Co., Ltd.	537	26%
85	JW Pharmaceutical Corporation	530	14%
86	Dongkook Pharm	519	9%
87	Sihuan Pharmaceutical Holdings Group Ltd.	510	43%
88	Kissei	493	-7%
89	Guangxi Wuzhou Pharmaceutical Group Co. Ltd.	490	-6%
90	Il-Dong Pharm	490	3%
91	Harbin Gloria Pharmaceuticals Co., Ltd.	488	10%
92	Toray Industries	483	-3%
93	Zeria Pharmaceuticals	479	70%
94	Nippon Kayaku	475	0%
95	Japan Lifeline Co., Ltd.	469	-2%
96	JCR Pharmaceuticals	465	65%
97	Xiangxue Pharmaceutical Co., Ltd.	461	3%
98	Hebei Changshan Biochemical Pharmaceutical Co. Ltd	460	34%
99	Mega Lifesciences Public Co. Ltd.	442	9%
100	Wockhardt	434	12%

CHINA TOP 20 PHARMACEUTICAL COMPANIES BY SALES

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13	CR Double-Crane Pharmaceuticals Co., Ltd	1413	15%
14	KPC Pharmaceutical Inc.	1280	14%
15	Zhejiang Huahai Pharmaceutical Co., Ltd.	1030	10%
16	Shenzhen Hepalink Pharmaceutical Group Co., Ltd.	987	28%
17	Zhejiang Conba Pharmaceutical Co., Ltd.	954	11%
18	Shandong Lukang Pharmaceutical Co., Ltd.	758	24%
19	SSY Group Limited	689	25%
20	Hualan Biological Engineering, Inc.	688	-6%

JAPAN TOP 20 PHARMACEUTICAL COMPANIES BY SALES

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15	Teijin Pharma	1672	20%
16	Nichi-Iko	1631	-7%
17	Towa	1411	-3%
18	Nippon Shinyaku	1099	3%
19	Hisamitsu	1095	2%
20	Kyorin	961	0%

SCRIP ASIA 100

INDIA TOP 10 PHARMACEUTICAL COMPANIES BY SALES

RANK	COMPANY	2021 PHARMA SALES ($M)	CHANGE FROM 2020 (% BASIS)
1	Sun Pharmaceutical	5199	15%
2	Aurobindo	3173	2%
3	Cipla	2939	15%
4	Dr Reddy's	2567	0%
5	Lupin	2191	7%
6	Zydus Lifesciences (earlier Cadila Healthcare)	2043	0%
7	Glenmark Pharmaceuticals	1665	13%
8	Torrent Pharmaceuticals	1139	5%
9	Biocon	1107	15%
10	Piramal Healthcare	907	16%

SOUTH KOREA TOP 10 PHARMACEUTICAL COMPANIES BY SALES

RANK	COMPANY	2021 PHARMA SALES ($M)	CHANGE FROM 2020 (% BASIS)
1	Celltrion	1671	6%
2	Yuhan Corp	1475	7%
3	Samsung BioLogics	1371	39%
4	GC Pharma	1344	5%
5	Chong Kun Dang	1174	6%
6	Kwang-Dong Pharmaceutical	1170	11%
7	Hanmi Pharm	1052	15%
8	Daewoong Pharmaceutical	1008	12%
9	SK Bioscience	812	0%
10	Dong-A Socio Holdings	771	16%

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ICON is the world's largest and most comprehensive clinical research organisation, but we're more than just a CRO. We know it requires more action beyond "status quo" in order to guide our customers through the ever-evolving landscape of clinical drug development. Powered by Healthcare Intelligence - the harmonisation of experience, expertise, insights, data, and technology - we strategically and proactively solve today's challenges without losing sight of their impact tomorrow.

From molecule to medicine, we advance clinical research providing outsourced development and commercialisation services to pharmaceutical, biotechnology, medical device and government and public health organisations. We develop new innovations, drive emerging therapies forward and improve patient lives.

ICON offers the most comprehensive suite of integrated clinical development services in the industry. We've designed fully customisable solutions to help our customers achieve their goals across a seamless delivery model spanning their product's entire lifecycle.

ICON has established relationships with a majority of the world's top pharmaceutical and biotech companies, offering:

Scale: With an expansive portfolio of integrated clinical, commercialisation and consulting services, global presence, depth in therapeutic expertise, and data-driven healthcare technology, we deliver globally scaled expertise & solutions for all customers and patients. ICON is:

- World leader in Functional Service Provision (FSP)
- Global number 2 in full service Ph 2/3 clinical research
- Global number 2 in Early Phase clinical research
- Global number 3 in Late Phase & RWE
- Global number 4 in Central & Speciality Laboratory Services

Focus: With no ownership from a parent organisation with different business lines or models, and no distractions from 'near adjacencies', we are completely committed to achieving clients' clinical development programs. Our 40,500+ employees have a singular focus on successful clinical research and commercialisation, leveraging transformational technology and innovation to execute clinical trials from Phase 1 to post-approval studies with the highest quality, expertise and speed.

Speed to market: Our extensive services portfolio, digital and data technology capabilities, and enhanced access to more diverse patient populations, have been combined with flexible delivery approaches and partnership models – all with the aim of reducing development time and costs.

Flexible partnership models: We have partnerships with a majority of the world's top biopharma and biotech companies worldwide. We are the global leader in Functional Service Provision and a top global provider of full service clinical research. Regardless of the size of your organisation or your project, we work your way.

Delivering integrated decentralised clinical trials: Clinical research should engage with patients wherever they are. ICON's customised, integrated decentralised clinical trial solutions can help you achieve better outcomes, while maximising recruitment and retention of diverse patient populations.

ICON has all the service components to deliver decentralised clinical trials and the experience and expertise to provide integrated, customised solutions.

Access to patients: Patients are at the heart of everything we do at ICON. We provide the most comprehensive and connected patient journeys across the largest and most diverse patient populations. Our site networks, patient recruitment expertise, and in-home services unlock access to millions of patients. ICON streamlines the clinical trial process, accelerating study-startup, and ensuring patient recruitment and retention meet or exceed targets.

ICON offers customers enhanced access to a larger global pool of more diverse patients through its global site network (Accellacare), specialised oncology network (Oncacare), a paediatric site network, in-home services and a network of six Phase I clinical research units across the United States and Europe.

Quality: The quality of our work is vital to our mission of bringing better medications to patients around the world. We are committed to maintaining, supporting, checking and improving our quality systems to exceed the quality standards demanded by our clients, patients and regulatory authorities. ICON's Quality Management System (QMS) comprises our mechanisms for ensuring that all our services are performed to the highest ethical standards, conform to all relevant regulatory requirements and satisfies contractual obligations.

Emerging therapies: ICON offers deep experience in the unique challenges of developing emerging treatments such as Immuno-oncology and other cell and gene therapies, with several approved treatments already on the market.

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MANUFACTURING

Lisa Takagi
Managing Editor, Japan

A Year's Struggle: How Japan Is Recovering Damaged Generic Supplies After Quality Violations

Japan struggles to recover its ever-expanding supply chain for generic drugs after several key players had their production stopped because of a series of GMP violations. As the share of generics grows under government policy, some in the industry argue the problems are deeply rooted in a decades-old pricing system.

The Japanese government and associations of domestic firms are trying to improve quality control and bring back stable distribution to the generics sector.

While the country has almost reached its volume share goal of 80% to reduce ever-rising healthcare costs, a supply shortage triggered by quality violations exposed in several generic firms has impacted patients and healthcare providers for over a year.

"We receive a prescription for a generic drug. It's out of our stock. We have no choice but to spend extra time and effort asking (both the patient and the doctor) if we can provide a non-generic alternative. Can't we put an end to this (cycle)?" tweeted a pharmacist in Japan on 16 March 2022 with a crying emoji. The post quickly gained more than 180 likes.

Posts like hers haven't been rare in the country since the beginning of 2021. Japan reimburses around 13,000 drugs under its national health insurance system, but the supply of more than 3,000 has been impacted, with 743 of these out of stock by September 2021, according to a report submitted to the government by the Federation of Pharmaceutical Manufacturers' Associations of Japan.

Although the government has been cautiously monitoring the supply chain and asking generic firms to recover this gradually, 82 products were still out of stock as of 12 April 2022, shows a list maintained by the Japan Generic Medicines Association (JGA).

QC VIOLATIONS, DEATHS, DISTRIBUTION CRISIS

The confusion in the supply chain started in December 2020, with the contamination of the oral antifungal Meek (itraconazole) from Kobayashi Kako Co., Ltd. with a high dosage of the hypnotic drug rilmazafone in the manufacturing process. Two patients receiving the product died and negative symptoms including dizziness and fainting occurred in 245 patients, of which 38 people had traffic accidents, according to the company's official website updated in March 2022.

Investigations by Japan's Pharmaceuticals and Medical Devices Agency and the local government triggered recalls of 30 products by Kobayashi Kako and six drugs from other generics firms including Aska Pharmaceutical Company Limited, Meiji Seika Pharma Co., Ltd and Elmed (previously known as Elmed Eisai), for whom Kobayashi Kako had been acting as a contract manufacturer.

After the incident, a series of investigations of manufacturing plants of generic firms all over the country by authorities ended up exposing violations of good manufacturing practice (GMP) by several domestic manufacturers. This led to several plant suspensions issued to major players; Nichi-Iko Pharmaceutical Co., Ltd. in March 2021, Choseido Pharmaceutical Co. Ltd. in 2021 and Kyowa Pharmaceutical Industry Co., Ltd in March 2022 over the use of undeclared materials and processes during production. (Also see "Nichi-Iko Suffers After Plant Closure" - Generics Bulletin, 28 May, 2021.) (Also see "Nichi-Iko Resumes Production After Suspension" - Generics Bulletin, 12 Apr, 2021.)

The impact was high. Under a policy to encourage the consumption of generics to contain healthcare costs, Japan doubled its volume share of such drugs from 2005 (32.5%) to 2017 (65.8%). According to the latest market report by the ministry of health, labour and welfare (MHLW) released in December 2021, that share had risen to 79%. Today, the MHLW is holding to its generic volume share goal of "80% by 2023" (the end of fiscal 2023 in March 2024).

WHAT CAUSED THE LONG-LASTING ISSUES?

On the other hand, GMP violations had already become an issue in the 2010's after several violations were exposed, although the MHLW had tightened its regulations on drug manufacturing and its quality control. For companies like Kobayashi Kako and Nichi-Iko, the pressure to keep their expanding production lines running with low costs won out over compliance, according to their investigative reports.

Kobayashi Kako coincidentally had expanded its manufacturing capacity more than 20 times from 2000 to 2019 and had issues in staff training and human resource planning which caused failure in quality management, according to an investigation report released in April 2021.

The report points out the company had several internal checkpoints in its manufacturing process intentionally skipped or mended, sometimes covered with false records. A couple of contaminations found before the rilmazafone incident were unreported or overlooked by busy plant staff to keep production on schedule. Although management was aware of the issue, reporting of updates to manufacturing processes to authorities were outweighed by other tasks to cut the manufacturing cost, the report states.

Another report from an external investigation of Nichi-Iko states the company had a similar situation. Internal warnings from staff who witnessed the illegal re-processing of unqualified materials had been ignored under pressure to supply products on schedule.

"The current pricing system and distribution were obviously the distant cause of those serious GMP violations," states a document released in February 2022 by the Japanese Society of Generic and Biosimilar Medicines in response to the generic crisis, although it condemns the management of the companies involved in violations.

Because Japan reimburses drugs' official prices to pharmacies and hospitals, there is a practice between these buyers and pharmaceutical companies to hold the real price lower than the reimbursement level for the buyers' benefit. Because the official prices of generic drugs are low from the beginning, pressures on generic firms to cut down the price and unit production cost – often in the manufacturing or distribution process - tend to be high, which could risk stable supply, the research states.

BUSINESS AND BUREAUCRATIC EFFORT NEEDED

After the series of incidents, both the government and associations of generic firms have made efforts to recover the stable distribution of generics while maintaining quality and safety.

The MHLW has listed 506 chemicals to be guaranteed stable supply for healthcare providers while closely monitoring the market. In December 2021, the ministry requested domestic pharma firms to lift the stock controls on 130 products; it is even planning to slightly raise or maintain prices if necessary, according to an explanatory document released in March 2022.

The local associations of generic firms are also enhancing their watchdog scheme to recover public trust in the market. In January 2022, the JGA ran self-checks of manufacturing plants belonging to 38 member companies by a third party, which found 31 out of 38 members, and 1,157 products out of 7,749, needed the re-filing of manufacturing processes to authorities, although association stated all the tested products' quality matched the legal criteria.

A Japanese Society of Generic and Biosimilar Medicines' proposal to prevent the reoccurrence of GMP issues lists three topics to focus on: enhancement of internal governance by pharma; tight GMP audits by authorities; and more reasonable pricing for generic drugs.

Suggesting tighter governance in pharma, the organization calls for "review and revision of current legal systems in drug pricing and distribution."

"Now that the share of generic drug is increased, it's inevitable to create systemic infrastructure to secure generic firms' production and (supply of) generic drugs as a social asset," it states.

A year after the Kobayashi Kako incident, Sawai Group Holdings, the parent of Japanese generic major Sawai Pharmaceutical Co., Ltd., announced the acquisition of Kobayashi Kako's production team to establish a new company, Trust Pharma Tech, a transaction completed on 31 March 2022.

The announcement states Trust Pharma Tech "will work on enhancing its compliance and quality control system to start shipping products in April 2023." (Also see "Sawai To Take Over Facilities Owned By Scandal-Hit Kobayashi Kako" - Generics Bulletin, 6 Dec, 2021.)

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MANUFACTURING

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Russia Sanctions, China Lockdown To Pinch Globally With Higher Freight, API Costs

With the Shanghai lockdown extended, Russian vessels blacklisted and oil prices fluctuating, global freight rates are expected to increase further. Apart from a direct hit, pharma manufacturers will also feel the ripple effect as prices of raw materials like APIs increase. Scrip spoke to Indian industry to gauge the impact.

Shanghai, the city with the busiest container port in the world, has announced an extension of a COVID-19 led lockdown. Meanwhile, the Ukraine crisis continues and Russia is expected to face additional sanctions, at least for now.

In today's connected world, the repercussions of such geopolitical developments are not constrained to those directly affected, as pharmaceutical manufacturers painfully discovered during the first lockdown in Wuhan and other cities in China in 2020.

Lloyd's List Intelligence data indicate that over 6,440 vessels are beneficially owned, operated or controlled by Russian interests, also indicating that 347 vessels have not moved since Russia began its incursion into Ukraine and at least 128 foreign-flagged ships are stuck inside Ukraine ports or anchorages.

War risk underwriters are imposing high insurance premiums on owners of vessels trapped in Ukraine while a general cargo ship is sinking after being shelled in Mariupol. EU Commission president Ursula von der Leyen has now announced a fifth round of sanctions against Russia.

Meanwhile, Danish shipper Maersk has said the Shanghai lockdown will severely hurt trucking services and increase transport costs. "Trucking service in and out [of] Shanghai will be severely impacted by 30% due to a full lockdown on Shanghai's Pudong and Puxi areas in turn until 5th April," the world's second-largest container shipping company said in an advisory before the partial lockdown was indefinitely extended to the entire city.

It had also notified clients that some depots and all warehouses in Shanghai will remain closed from 28 March until further notice.

Though the city has so far managed to keep its deep-water port and airports open, movement on its streets are severely curbed. Shanghai International Port Group, which runs the facility and leases containers, has implemented a closed-loop system within the port, which means employees are to live and work on the premises. (Also see "Uncertain Times: New Lockdowns, Ukraine Challenge Chinese Pharma" - Scrip, 24 Mar, 2022.)

However, COVID-19 test protocols are hindering trucks and barges from handling cargo, with drivers being turned away unless they provide a negative test result within the prior 48 hours. Besides, they are to quarantine on return from Shanghai.

In addition, oil prices have been on an upward trend, which is expected to increase global land transportation costs even further. Statista.com shows the OPEC basket stood at $19.70 per barrel on 14 April 2020 with Brent crude at $29.6 a barrel. In comparison, the OPEC basket was at $106.23 and Brent at $107.53 a barrel on 4 April 2022.

The combined impact is expected to see global freight rates rise further even as pharmaceutical manufacturers have dealt with increased costs since 2020. (Also see "Global Uncertainty Is Impacting Deal-Making, Investment Decisions" - Scrip, 1 Apr, 2022.)

INDIA BETTER PREPARED

Ashok Madan, executive director at Indian Drug Manufacturers' Association (IDMA), with over 1,000 members including small and medium enterprises, told Scrip "all these developments will definitely have an impact, but the extent will depend more on how the situation changes in China. We are keeping a watch."

Like several other countries across the world, India imports raw materials like active pharmaceutical ingredients (API), intermediates and excipients from China. However, it has a disproportionate dependence, even up to 100%, for certain APIs. (Also see "India Steps Up Scrutiny After Chinese API Prices, Military Tensions Rise" - Scrip, 3 Jul, 2020.)

Nevertheless, Madan pointed out that compared to 2020, Indian companies are better prepared this time around. In 2020, apart from the partial lockdowns in China, India itself went into a complete shutdown, though after initial hiccups, classification of pharma as an essential industry allowed it to service customers in and out of the country.

Sudarshan Jain, secretary general of Indian Pharmaceutical Alliance (IPA), which counts India's largest firms among its members, told Scrip "the learning of the last two years has been great. We are keeping inventories of 30-45 days of APIs [active pharmaceutical ingredients] and the large pharma companies have three to four months of finished goods stock."

While the Indian government began an attempt to decrease the industry's heavy dependence on China for APIs and intermediates, the benefits will take time to show, both Jain and Madan felt.

In 2020, the government introduced a INR69.4bn ($917.6m) profit-linked incentive (PLI) scheme for production of certain critical raw materials like penicillin G following which an INR150bn PLI scheme was notified in March 2021 for makers of certain complex formulations, excipients, phytopharmaceuticals, capsules and even invitro diagnostic devices.

> "All these developments will definitely have an impact, but the extent will depend more on how the situation changes in China. We are keeping a watch."
>
> – Ashok Madan, Executive Director, IDMA

"It will take around two to three years from a long-term perspective for the situation to resolve meaningfully. While this government understands the problems we face and has taken active steps to help, we can't change things overnight," IPA's Jain said.

IDMA's Madan concurred, saying the government "is alive to our needs and the industry has never received this level of funding before." However, since higher incentives have been provided to greenfield projects, the benefits will take time to flow down.

Brownfield projects have also received support, but the "level of incentives is 5% compared to 10% for greenfield ones. If existing units had been revived with government help and received tech-

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nology support from bodies like CSIR [Council of Scientific and Industrial Research], we could have achieved self-sufficiency in APIs and other materials faster," he pointed out.

SRI LANKA, PAKISTAN ADD TO TURMOIL

While API prices are expected to rise in the short term and could erode companies' profits when inventory runs out, the Russia-Ukraine turbulence could paradoxically also lead to higher sales for some.

"With Russia facing sanctions, it would not like to buy pharma products from multinational companies (MNCs) and given historically good relations between the countries and our manufacturing caliber, it is likely to turn to Indian companies," Madan noted.

MNCs have so far maintained supply lines for medicines to both Russia and Ukraine. Any company conducting business in these two countries can, however, expect payments to be delayed. (Also see "Europe's Generics Industry Takes Action To Maintain Medicines Access In Ukraine" - Pink Sheet, 2 Mar, 2022.)

Front-line Indian firms such as Sun Pharmaceutical Industries Ltd., Dr. Reddy's Laboratories Ltd. and Glenmark Pharmaceuticals Limited are among those with significant activity in the Russia-Commonwealth of Independent States CIS) region. (Also see "Turbulence Ahead For Indian Firms Caught In Russia-Ukraine Conflict" - Scrip, 3 Mar, 2022.)

Meanwhile, the political situation in neighboring Pakistan is deteriorating by the day. The country's Supreme Court is expected to rule on the legality of political exercises leading up to Prime Minister Imran Khan's dissolution of the national assembly and a call for fresh elections.

Sri Lanka has had an economic meltdown with the crisis forcing people to come out on the streets in protest against crippling power cuts and essential commodities' shortage. After imposing a state of emergency, President Gotabaya Rajapaksa revoked it late on 5 April. The ruling coalition appears to have lost majority in the 225-member Parliament, with over 40 MPs declaring themselves independent.

Apart from large Indian companies like Sun Pharma and Cipla Limited, several smaller companies also operate in Sri Lanka. Despite animosity between India and Pakistan, pharmaceutical products are also supplied to the neighbor.

"The RBI (Reserve Bank of India) is evaluating options" to secure payments to Indian companies in Sri Lanka, IPA's Jain told Scrip.

Brian Yang
Managing Editor

Pharma Will Need To Embrace More Inward-Looking China

The world's second-largest economy is fast moving away from reforms and open to a "dual circulation" model, focusing on domestic market consumption while reducing export-driven production. Executives and investors shared views at a conference on whether multinational pharma firms are still welcome in China and what opportunities may lie in the drastic policy shift.

In China's Fourteenth Five-Year Plan for the 2020-25 period, President Xi Jinping outlined a new and bold economic policy move - moving away from a four-decade policy of fundamental reforms and opening to the idea of "dual circulation", comprising domestic consumption and international trade and investment.

Unlike the previous focus on export-driven production, under which the country became known as the "world's workshop", the new policy prioritizes rebalancing in the home market while remaining open to the flow of external goods and funds. The shift is a direct response to the widespread global economic downturn and ongoing US-China trade tensions.

The strategic goals are to rely more on driving supply-side demand, encourage domestic collaboration and reduce the impact of international economic risks. However, the change, when announced, immediately put on alert foreign corporate players in China, where many have now operated for decades. Would it mean multinationals are no longer welcomed?

The dual circulation policy will indeed require companies to go "more local" in China, Claudia Süssmuth-Dyckerhoff, a board member of Swiss pharma and diagnostics group Hoffmann-La Roche Limited, told a panel discussion of the Asia Summit on Global Health, held in Hong Kong and virtually on 24 November.

"Localize more in China," advised the executive, who said the policy clearly indicates China is focusing more on building and expanding local supply chains. Roche Diagnostics has already taken some steps in this direction, opening a manufacturing plant in Suzhou and a drug innovation center in Shanghai, while a local innovation accelerator initiative is planned in the next quarter, she noted.

Another component is pharma innovation, which is already on the rise in China and indicates the growing importance of home-grown R&D. In 2020, for example, 44 innovative new drugs were approved in the country, of which 17 were locally developed. More companies are pursuing an "in China for China" development strategy and some are even choosing China as their first launch market, in turn indicating progress in the regulation and market acceptance of such products domestically.

Executives from China National Biotec Group, Roche, Qiming and WeDoctor in the ASGH panel discussion. Brian Yang/Scrip.

Some smaller foreign biotech companies are also particularly eager to gain access to the Chinese market, even if these means choosing a non-local partner. In one notable example, US firm FibroGen, Inc. linked with AstraZeneca PLC to launch its chronic kidney disease anemia drug roxadustat in China, where the HIF-PH inhibitor had its first global launch.

Meanwhile, many Chinese firms are now at the stage when they can out-license their novel immuno-oncology and cell therapy assets to US partners, noted Nisa Leung, a managing partner at Qiming Venture Partners. Half of the fund's $6.2bn raised so far has been in healthcare and the speed at which the sector has become a central theme has been "stunning", she told the summit.

PRICING, ACCESS CHALLENGES

But there was a view at the Hong Kong meeting that, despite the rapid development and innovation spur, the policy of dual circulation won't substantially change the Chinese government's price-cutting approach to the healthcare sector.

In a bid to make innovation affordable, Beijing has regularly resorted to volume-based procurement mechanisms and annual price negotiations to pressure manufacturers to cut product prices, which can routinely exceed 50%. This has caused

CHINA

many international pharmas to walk away from procurement rounds, citing unsustainable pricing levels.

But Süssmuth-Dyckerhoff suggested the need for expanded access to care should not rely solely on price cutting. "We work with the government for additional insurance [programs] and not just [the government] asking for very low prices," she told participants in the conference, held in a hybrid online and offline format.

"We should come together to make innovation accessible through innovative insurance schemes," she proposed.

CHINA ON OWN TRAJECTORY?

The meeting also heard that dual circulation, despite its intention to link internal and external economic drivers, may potentially put China on its own track apart from others in the post-pandemic world.

While many other countries are adopting a policy of living with the coronavirus, China is steadfastly continuing with a "zero-COVID" rule and imposes strict lock-downs and testing in communities where just a single case is identified. While such restrictions are creating many uncertainties, the over-arching demand for better care will continue to grow, speakers at the conference agreed.

In a country where five million cancer cases are diagnosed each year, double that in the US, the strong medical need will translate to more simultaneous drug studies in China and the US, shortened approval lag with other major markets and emerging new companies and therapies.

There has already been a jump in the local development of gene and cell therapies and lower costs are likely to mean such promising new treatments will be more affordable, predicted Qiming's Leung.

DATA PROTECTION UNCERTAINTIES

Nevertheless, concerns remain around China's tightening grip over privacy and data protection, and some recent regulations may be pushing foreign players away from developing their latest therapies.

"Data protection is very difficult" and creates "uncertainties" for overseas players like Roche to develop gene therapies in China, noted Süssmuth-Dyckerhoff. Roche acquired gene therapy developer Spark Therapeutics, Inc. in 2019 and has signed a global licensing deal with Sarepta Therapeutics, Inc. for the Duchenne muscular dystrophy gene therapy SPR-9001.

But China requires the collection of all data relating to genetic information, including blood samples and genomic data, which should be stored and processed inside the country. The export of such data requires going through and administrative approval process.

Recent rules further require foreign entities to establish designated agencies or representatives in China to handle matters related to the protection of personal information. The scope of personal information includes biometrics that could identify a specific natural person alone or in combination with other information.

Despite the potentially revolutionary nature of gene therapies, the very strict rules governing the use of data potentially shut out foreign investment out, said Süssmuth-Dyckerhoff, expressing a hope that authorities will "lower the barrier to encourage data exchange."

CLOSURE TO CONTINUE?

China's increasingly inward-looking policy shift and pandemic policies also mean the country could potentially remain closed to outside visitors for the foreseeable future.

The government has yet to approve a more effective mRNA COVID-19 vaccine and protection from the current crop of inactivated virus-based vaccines may have waned substantially. As other major economies including the US and Japan start to reopen, China remains effectively shut off to international travel and strict community lock-downs.

This situation is deterring much foreign talent from returning to China and conferences with international participation continue to be held mostly online. The globalization in talent and need for person-to person exchanges should "see more scientists meet in person," urged Süssmuth-Dyckerhoff.

'Booming' China Pharma R&D Reaches New Peak

Brian Yang
Managing Editor

China has emerged as a major new force in global pharma R&D amid a "boom" in activity, with not one but two of its companies entering the top 25 by pipeline size for the first time.

While China is a relative latecomer to the global pharma R&D party, some of the fastest pipeline growth is now coming out of the country, which for the first time also has several home-grown entries ranking among the world's top 25 pharma companies by pipeline size.

"For the first time, we see not one, but two Chinese-headquartered companies have left the runway and entered the stratospheric heights of pharma R&D," author Ian Lloyd notes in a new Pharmaprojects report. Jiangsu Hengrui Medicine Co., Ltd. soared from 37th place the previous year to rank at 16th, fueled by a colossal 71.2% increase in its R&D portfolio size.

The Liangyungang, Jiangsu province-based drug maker, known for its stance of sticking to its own in-house R&D and innovation, has transformed from being chiefly a generics maker to producing novel assets including an immuno-oncology anti-PD-1 antibody, a PARP inhibitor and cardiovascular drugs. (Also see "Hengrui Takes Focused Approach Amid China Inc's Global Drive" - Scrip, 23 Dec, 2021.)

Another quick riser in the ranking was Shanghai Fosun Pharmaceutical (Group) Co., Ltd., which "makes an even steeper ascent, surging 43 places upwards with a pipeline swollen by 127%," Pharmaprojects' senior director Lloyd notes in the Pharma R&D Annual Review 2022, published by Citeline (part of Informa Intelligence). Unlike Hengrui, Fosun has relied mainly on licensing in assets from partners, including BioNTech SE for its mRNA COVID-19 vaccine.

Major Chinese firm BeiGene, Ltd., meanwhile, is perhaps best known known for its multi-billion dollar alliances with Amgen, Inc. and with Novartis AG for the PD-1-targeting antibody tislelizumab. It ranked among the world's top 20 pharma companies in terms of rare disease drug pipeline and 26th overall.

These developments present "something of a landmark moment for Chinese pharma R&D," Lloyd noted in the report, which is based on a snapshot of data as of 4 January 2022.

> For the first time, we see not one, but two Chinese-headquartered companies have left the runway and entered the stratospheric heights of pharma R&D."
>
> - Ian Lloyd

'BOOM' IN CHINA R&D

Although the figures for each individual Chinese company may look stellar, it is the overall upcoming ecosystem in China that is helping sustain the strong growth, the review states.

While the US has long been cherished as a hub for medical innovation, sustained by clusters of emerging startups and R&D centers. China is now going through the same energetic growth phase. The number of China-based pharma firms jumped from 9% to 12%, while those headquartered in the US fell by 2%, with the number of Chinese pharma companies with R&D activities jumping by an "astounding" 43.3%, from 522 to 792.

This was a "very significant expansion for a single year," noted Lloyd. "There is truly a boom in R&D going on there."

While the US continues its dominance, accounting for 53.4% of all drug R&D development activities globally, China came in second with 20.8%. "All in all, this represents something of a landmark moment for Chinese pharma R&D."

CELL, GENE THERAPY PRESENCE

China's growing presence in the emerging regenerative medicines space, including gene and cell therapies, also has many taking a fresh look at its potential in these treatment frontiers.

The country had the second-largest number of clinical study registrations for cell therapies, including in the CAR-T, NK cell and BCMA-targeting fields. One home-grown company, Legend Biotech Corp., along with partner Johnson & Johnson, recently scored a landmark US approval for its BCMA-targeting cell therapy Carvykti (ciltacabtagene autoleucel).

In gene therapy, armed with venture capital funding and US-trained scientist returnees, China could see breakthroughs in adeno-associated virus vector approaches for hemophilia A and B and Leber hereditary optical neuropathy.

RIDE NOT TOTALLY SMOOTH

But all this rapid progress doesn't mean that China's pharma R&D ride will be quick and smooth without turbulence. Despite having a large unmet medical demand and population, the country faces key issues around a lack of source innovation and R&D infrastructure, mRNA COVID-19 vaccines presenting a prime example.

Despite massive investment and know-how from an ex-Moderna, Inc. scientist, China has yet to produce a domestically-developed jab in the class.

With none of these highly effective vaccines yet available in China, some parts of the country have had to move back into lockdown as cases rise, including the strictest restrictions so far in its largest city, Shanghai. The city's 21 million people are under five-day house quarantine in two phases from 28 March, depending on results of mass testing. The city's vast public transportation system is being shut down during the period.

More widely, the Pharmaprojects report points to lower new drug R&D productivity and lack of momentum for big pharma firms, with mid-sized operations doing most of the heavy lifting. 14 of the world's top 25 pharma companies by pipeline size reported their pipelines contracted in 2021. The top 10 companies yielded only 4.6% of drugs, a new record low, and the top 25's share of total new drugs fell to 8.51%, less than half the figure a decade ago.

Access the full Pharma R&D Annual Review 2022 report here.

Ian Haydock
Editor-in-Chief, APAC

Taiwan 'A Great Place' For Clinical Trials, But Tweaks Needed

Amid simmering regional geopolitical tensions, speakers at a recent conference highlighted the multiple benefits of conducting clinical trials in Taiwan, while pointing to what more could be done to improve the local ecosystem.

Taiwan may be dominating global headlines this week over the reactions to US House Speaker Nancy Pelosi's controversial visit, but for the global pharma industry already operating there, it was issues around local clinical trials that came into focus at a recent conference.

The island has long been viewed by the international pharma industry as having international-level investigator expertise and facilities, with R&D executives citing in the past factors including a dense population of 23.6 million and higher incidence of certain diseases like nasopharyngeal carcinoma.

In fact, the business models of some companies such as Singapore-based ASLAN Pharmaceuticals Pte Ltd, which focuses on oncology, includes leveraging high-quality and generally lower cost clinical sites in Asia - such as Taiwan - to progress their pipeline assets in a cost-effective way.

These considerations and others were reinforced in a session on international collaboration strategy at the BIO Asia-Taiwan meeting, where participants heard that "Taiwan is a great place to do clinical studies" - but also that there's still scope for multiple improvements.

Introducing the session, Henry Chen, president of local group IRPMA (the International Research-Based Pharmaceutical Manufacturers' Association) and general manager of Chugai Pharmaceutical Co., Ltd. Taiwan, observed the innovative pharma industry "highly appreciates the continuation of the friendly biotech environment in Taiwan."

The island boasts "comprehensive health data, world-class capabilities in ICT [information and communications technology] and high-quality medical standards."

But it is now "at the intersection of challenges and opportunities" and faces a critical time to pursue public-private partnerships that would position is as a global leader, he told the 27-29 July hybrid event, held ahead of Pelosi's 2-3 August visit.

STRONG GROWTH IN STUDIES

GSK plc Taiwan general manager Mick Stanley, speaking for the IRPMA – which represents multinational research-based firms in Taiwan – elucidated the pros and cons of carrying out trials in Taiwan, highlighting a number of areas where the group would like to see changes.

On the plus side, Taiwan has well-developed "expertise, primary investigators and medical institutions." These all contributed to a 16% increase in the number of Phase III trials conducted in 2021 to 88, with immunology and oncology the main focus areas, based on a survey of 21 member companies.

80% of the total were sponsored by MNCs and 90% were multinational studies which included sites in Taiwan, which Stanley said was testament to Taiwan's capabilities.

The total number of local trials (of all phases) is expected to hit 260 this year, versus 152 in 2021.

Taiwan does an "excellent job" on quality, speed and enrolment, as part of which there are robust audits and inspections and adherence to International Conference on Harmonisation Good Clinical Practice standards, the GSK executive told the meeting.

> [The payer database] is a really good area that Taiwan does great with...and is a differentiator for Taiwan."
>
> - Mick Stanley, GM, GSK Taiwan

The payer under the universal healthcare scheme also has a strong database. "That's a really good area that Taiwan does great with...and is a differentiator for Taiwan," Stanley said, pointing to the support for real-world data the information provides.

"We need to continue to look into those databases and the feasibility of adding to clinical studies."

ROOM FOR IMPROVEMENTS

While there have been multiple regulatory improvements, he pointed to several areas where the IRPMA would like to see additional enhancements to further streamline processes.

While some complexity is required to ensure appropriate oversight of trials, investigators at present need to work with different departments under the Ministry of Health and Welfare to get trial approvals off the ground, which "most of the time are not talking to each other."

This means it can take around a year of "administrative back and forth" to set up a study, and a solution here may be to consider establishing a single unit or "a taskforce with a vision" to improve oversight of trial approvals.

In addition, there is at present no overall accreditation scheme for clinical research professionals in Taiwan. Another area for attention would be reductions in the local documentation requirements (for instance for institutional review board submissions) to align with international best practices.

For enrolment, the use of new digital tools may help boost this, along with use of existing data and other appropriate incentives. More generally, Stanley also pointed to a need for authorities to consider more tax, funding or other incentives to make it even more attractive for companies to conduct trials in Taiwan, akin to those offered by Australia.

One positive from the requisite level of complexity for effective trial oversight is the need for related services such as site management and laboratory analysis, which Stanley noted could help create high-quality skilled employment opportunities.

The overall message from the IRPMA is that "we want to work together with the government" in seeking the outlined changes, he stressed.

WIDER POST-PELOSI FALLOUT?

Separately, whether there will be wider fall-out from the Pelosi visit beyond mainland China's immediate responses that could affect the regional biopharma industry remains to be seen.

China has so far implemented import/export sanctions on selected products traded with Taiwan and also initiated multiple live-fire military exercises all around the island. Some observers are also predicting a shift in focus for Taiwanese companies in the sector away from the mainland as cross-strait relations continue to come under strain by such actions. (Also see "China-US Tensions Rise Sharply On Pelosi Visit, Will Biotech Get Burned?" - Scrip, 3 Aug, 2022.)

China and Taiwan already have several important cross-strait agreements, both signed in 2010 – an Economic Cooperation Framework Agreement, which cut tariffs, and the Cross-Strait Medical And Healthcare Cooperation Agreement.

However, the first is generally seen as having lagged and not met its strategic objectives, while the latter called for more targeted cooperation in areas including infectious diseases and medical product specifications, for example, while maintaining restrictions on medical practice interactions and hospital investments.

The healthcare agreement also provided for the mutual recognition of clinical data from selected designated medical facilities on both sides, although this was limited in scope. Helped by this, some Taiwanese companies, including Medigen Biotechnology Corp., have in the past initiated Phase III programs on the mainland supported by Phase I/II data from Taiwan.

More broadly, the cross-strait economic interlinks are substantial, particularly in the high-tech and semiconductor sectors, with all Taiwanese investments on the mainland estimated to total around $60bn. It is so far unclear whether additional measures impacting these are being considered.

Anju Ghangurde
Executive Editor, APAC

Bayer's Koenen: Decentralized Trials For Pivotal Studies Not 'Black Or White Scenario'

A cross-section of biopharma experts including senior executives of Bayer, Boehringer Ingelheim and Accenture and US FDA Director at the India Office deliberate digitization and evolving trends in clinical research, including the potential of decentralized trials and metadata-driven automation.

High-profile industry experts and regulatory officials discussed, at a recent summit, a range of issues around trends in clinical trials including the role of digital technologies, metadata-driven automation and also real world data and predictive evidence in insight generation.

Addressing the annual summit of the Organization of Pharmaceutical Producers of India (OPPI), Dr Christoph Koenen, global head of clinical development and operations, Bayer AG indicated that clinical trials will remain a "cornerstone" of evidence generation of the future but with a shift to decentralized clinical trial (DCT) approaches.

"The whole idea of DCT as a concept is not going to change, but the technology you can use to successfully collect data in DCT is constantly going to evolve, and therefore going to change the pace of DCTs over the next coming years," Koenen said at the virtual event.

Koenen also observed that while currently the acceptance of DCT-collected data for pivotal studies varies depending on "which regulator you talk to", there is some skepticism around whether the data/end points collected using DCT has the same degree of quality as the traditional brick and mortar approach.

"That is the reason why you do not see right now completely DCT-run pivotal studies yet," declared Koenen, who took charge in his role at Bayer in January this year moving from Otsuka Pharmaceutical Co. Ltd., where he held the position of Chief Medical Officer.

Regulators have, on their part, urged industry to talk to them or others with experience with DCTs, and ensure that such dialogue occurs early.

NOT A 'BLACK OR WHITE SCENARIO'

Nonetheless the Bayer executive believes that as industry's experience and confidence with DCTs grow and evolve, their acceptance for pivotal studies will also increase.

"However, it might not be a black or white scenario where you will have a study that is done 100% brick and mortar and 100% DCT; we might find ourselves in a situation where we have a certain percentage of patients participating in the study by a DCT approach and then you might have certain percentage of patients that will participate in the study by a brick and mortar site," Koenen explained.

The advantage of having this flexible approach, he said, is that you can make the participation in the DCT approach dependent on a specific patient's "living situation - how is the access to technology/ data connection/home care - and you can take a very flexible approach."

Earlier McKinsey & Co noted that the shift of trial activities closer to patients has been enabled by a constellation of evolving technologies and services including tools such as electronic consent, telehealthcare, remote patient monitoring, and electronic clinical-outcome assessments which enable investigators to maintain links to trial participants without in-person visits.

The management consulting firm also indicated that the fully virtual model is gradually migrating from smaller, early-phase and post-approval studies towards larger pivotal trials.

"Nonetheless, in the near term, sponsors, investigators, and research-service providers expect fully virtual trials to remain limited to a narrow set of use cases, such as a well-characterized drug with few adverse events in a mild indication, with end points suited to remote measurement," McKinsey executives said in a June 2021 article.

Kailash Swarna, managing director and global leader, clinical development, Accenture Life Sciences, who moderated a session on "Disruptions and Digitization Trends in Clinical Research" at the summit, highlighted how COVID-19 catalyzed systemic changes in clinical development and organizations have been forced to lean into virtual methods, leading to an increase in competency and investment in digital health.

On DCTs, he put forth that if industry could engender "confidence" in terms of using technology appropriately, "imagine what we could do in terms of bringing more patients into the clinical trial landscape". Ultimately the goal, he emphasized, is to make clinical development and clinical trials part of the continuum of care.

"So we actually see that from clinical trials to the practice of medicine there is continuity on how we can bring treatments to patients."

The clinical trials segment has been fraught with challenges such as low trial participation and recruitment, poor engagement and retention and high costs. Data from Accenture suggested that 86% of clinical trials do not meet enrollment timelines while 30% of participants identified do not complete the study on average.

DIGITAL HEATH TECHNOLOGY - "FIT FOR PURPOSE"

Dr Sarah McMullen, director, US FDA India Office, touched upon aspects of leveraging different types of digital health technology (DHT) tools in the conduct of clinical trials.

McMullen urged sponsors to ensure that a DHT is "fit for purpose".

"This can mean asking and answering questions such as is the tool reliable and appropriate to that context? Is the data to be captured valid to the intended research question? Is the consent process adequate for describing the risks of the use of this technology to the participant? And can it also be ensured for traceability from end-to-end usage and its main consideration for data integrity," McMullen explained in the panel discussion at the OPPI summit.

In addition, the regulatory official also referred to cyber security risk, noting that most people have been probably impacted in some way in their lives by "some sort of cyber security risk or malfeasance in that area as well".

In December last year the FDA had introduced a draft guidance "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations" ; it provides recommendations to sponsors, investigators, and other stakeholders on the use of DHTs to acquire data remotely from participants in clinical investigations evaluating medical products.

The guidance suggests that sponsors should ensure that the level of validation associated with the DHT is sufficient to support its use and interpretability in the clinical investigation. (Also see "FDA Draft Guidance Paves Way For Collecting Clinical Study Data Via Digital Health Technologies" - Medtech Insight, 22 Dec, 2021.)

CLINICAL TRIALS

BALANCE BETWEEN DIGITAL INNOVATION AND DISRUPTION

Significantly, though, panelist Dr Vijay Prabhakar, head of therapeutic area, clinical development and operations at Boehringer Ingelheim, emphasized that not every patient potentially "likes" DCT and it is important to understand that the choice at the end of the day lies with the patient and the investigators.

"We shouldn't sometimes assume that anything digital is going to reduce complexity, because sometimes digital could also increase complexity. This is where at some point in time, we need to strike a balance between what we need as digital innovation versus being too disruptive that it becomes inconvenient for the patients and investigators," Prabhakar said, among a string of other comments. Regulatory considerations pertaining to digital health technology were also part of the panel discussion.

The BI executive, though, sees a lot of untapped potential despite the pandemic, for instance "lot of future" in artificial intelligence speeding up adjudications, helping people adjudicate endpoints faster using radio mics. (Also see "Considerations For Using Established Versus Novel Endpoints In Decentralized Trials" - Pink Sheet, 18 Mar, 2022.)

"There are so many options that are still not being used," said Prabhakar, a physician trained in intensive care and emergency medicine.

Clinical endpoint adjudication is a standardized process for assessment of safety and efficacy of pharmacologic or device therapies in clinical trials.

The McKinsey article referred to previously also highlighted the need to balance the needs of each stakeholder group in DCTs and provide them with a "positive, differentiated" experience. Patients, it noted, vary in their comfort with and access to technology and preferences for in-person physician visits versus visits by phone or video. "Patient-centric trial design is critical to mitigating such concerns. It can include, for example, patient training and support, user interfaces tailored to specific patient groups, and the option to choose between a decentralized arm and a conventional arm."

ASUNDEXIAN PROGRAM

Meanwhile Bayer's Koenen also spotlighted the German group's clinical trial approach for the investigational drug asundexian, where it is utilizing various innovative approaches.

Asundexian is an oral inhibitor of Factor XIa being developed as a potential treatment for secondary prevention in patients with a non-cardioembolic ischemic stroke as well as for atrial fibrillation and recent myocardial infarction.

The global head of clinical development and operations outlined how the program has a certain percentage of patients in the US where the DCT approach is used. "We have an agreement with global regulatory authorities that we can use some percentage of patients in this program - we collect the data using the DCT approach."

The program has also used registries to identify patients that can potentially enter the study, therefore making sure that patients with the "right patient characteristic" are approached in order to be included in the trial, and "we do identify those patients in advance." The German multinational is also automating processes of the study "as much as we can" in order to improve the quality as well as the speed that it takes to conduct the trial, he added.

Asundexian is currently being studied in the PACIFIC Phase II clinical trial program that consists of three Phase IIb studies in over 4,000 patients with one of the three medical conditions: atrial fibrillation, a recent non-cardioembolic ischemic stroke or a recent myocardial infarction. It is being studied in all three indications either as a standalone therapy, or in combination with anti-platelet therapy. (Also see "Xarelto Still Climbs As Bayer Touts Successor" - Scrip, 1 Mar, 2022.)

METADATA DRIVEN AUTOMATION

Koenen, who has held senior leadership positions in clinical development at GlaxoSmithKline plc, Novo Nordisk, and Bristol Myers Squibb Company along his career journey, underscored the value of using metadata-driven automation to increase efficacy in how trial processes are run; currently these involve significant manual work which is time consuming and also "introduces quality risk."

"If we standardize it, automate this as much as we can and automate the generation of different documents, be it part of the protocol, be it part of the study report, then the quality of documents that we produce will improve and the time it takes to produce these documents will be much less," he emphasized.

As technology evolves - artificial intelligence is expected to play a very important role – the ability to advance such efforts increase, he added.

REAL WORLD DATA, PREDICTIVE EVIDENCE

The Bayer executive also touched upon the growing importance of real world evidence, currently largely used to look at outcomes of different therapeutic approaches in a real world, mostly after drugs have been approved.

"What will happen is that the importance of real world evidence is going to increase and we will increasingly rely on real world evidence to make, for example, regulatory decisions around efficacy and safety as well."

He predicts that world is likely going to shift from a more traditional approach of using mostly trial evidence to make decisions to one that will use different kinds of evidence in order to make decisions. "In the future, real world data and predictive evidence [will] play an even more important role in the insight generation mix."

Koenen, however, cautioned that such evidence can only be used if "we are sure that we are collecting, processing, analyzing and interpreting all these different kinds of evidence appropriately, and we have to make sure that we have the systems in place in order to do that."

"What will happen is that the importance of real world evidence is going to increase and we will increasingly rely on real world evidence to make, for example, regulatory decisions around efficacy and safety as well."

– Dr Christoph Koenen, global head of clinical development and operations, Bayer AG

He also noted that with the use of digital technology in clinical trials alone, the volume of data industry is collecting is going to "explode" and referred to the example of home monitoring and having a patient wear three-lead ECGs (electrocardiograms).

"What if you have a patient wears this for a long, extended period of time? What if you start monitoring sleep, breathing pattern, pulse pressure in your clinical times and over a certain period of time? Imagine the amount of data that you have to collect and store and process in order to do that."

Hence, it's important for industry to create advanced analytics and data ingestion platforms to handle that.

"So it's our ability to store and collect data and then the ability to process the data, and then make sure that we analyze the data in an appropriate way to draw the right conclusions," he added. With increasing volume of data, data handling capabilities need to be further strengthened, he underscored.

JAPAN

Lisa Takagi
Managing Editor, Japan

Sawai Urges Japan To Take 'Best And Only Chance' To Reform Pricing Amid Generic Crisis

Kenzo Sawai, president of Japanese generics giant Sawai Pharmaceutical, tells Scrip in the first of a two-part exclusive interview about the firm's strategy and backstory of efforts to maintain product supplies amid the country's ongoing generic crisis. He also urges Japan to take "the best and only chance" to reform its drug pricing system to help the entire market survive.

"The damage caused by a couple of players in the generic industry ended up blocking other players' distribution in its course of recovery."

Describing the generics crisis that has been haunting Japan's pharmaceutical industry for more than a year, Kenzo Sawai, president of one of the country's biggest firms in the sector, Sawai Pharmaceutical Co., Ltd., told Scrip the challenges had created "the biggest and the only chance to seriously discuss the reformation of Japan's drug pricing system."

In an exclusive interview at the company's headquarters in Osaka, Sawai talked about the factors potentially extending the challenges of the industry and which elements in the current system he thinks should be reformed to ensure its long-term survival.

(The second part of this two-part interview focuses on Sawai's business strategies and international expansion and is available here.)

GENERIC CRISIS' IMPACT ON SAWAI

Although Sawai has maintained its products' quality while regularly making new launches in the market, the firm has been one of many in Japan's generic sector obliged to limit distribution of some lines, even while making efforts to expand capacity during the crisis.

This started in late 2020 following contamination problems with a product from Kobayashi Kako, which triggered recalls and the discovery of other GMP violations (see side box). (Also see "A Year's Struggle: How Japan Is Recovering Damaged Generic Supplies After Quality Violations" - Scrip, 12 Apr, 2022.)

As of 22 June, the firm had 347 products for which shipments had been limited and 22 for which shipments had been stopped, mainly because of uncertainty of supply from its contract manufacturers.

"The situation has become better, by this April we lifted stock limitations on more than 100 products," he said. "However, as for products with larger needs, it will take time to get them back to the normal pace of supply. We have to be extra careful [to measure the balance between the market's needs and the volume of products' stocks]."

Sawai told Scrip the incidents at Kobayashi Kako and Nichi-Iko Pharmaceutical Co., Ltd. had both hit him by surprise. Nichi-Iko's case made him assume "there should have been difficulty in maintaining so many product lines and confusion and cost issues possibly followed." While local authorities tightened GMP inspections, Sawai immediately checked its own manufacturing sites and production facilities to identify any room for betterment.

In fact, the firm enhanced its logistics facilities in 2021. It also acquired a manufacturing site from Kobayashi Kako and started a new company called Trust Pharmatech to manufacture Sawai products.

ONGOING GENERIC CRISIS IN JAPAN

The generic crisis was triggered by a series of good manufacturing practice (GMP) violations by Kobayashi Kako and Nichi-Iko since the end of 2020, which has impacted the production of distribution of more than 3,000 generic products out of around 16,800 in the domestic pharmaceutical industry.

3,080 products have had their distribution limited or halted as of March 2022, according to the latest survey by the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ).

INDUSTRY FACING TRUST DEFICIT

Following the incidents, nationwide inspections by local authorities resulted in a couple of generic firms with confirmed GMP violations including Choseido Pharmaceutical Co. Ltd. and Kyowa Pharmaceuticals being given plant suspensions. Soon, the growing needs from the market and the complex nature of the industry, where many companies provide contract development and manufacturing functions to each other, triggered stock shortages of many products.

STOCK SHORTAGES IMPACT SECTOR

According to the FPMAJ survey, as of mid-May 2022 449 products had limited shipments for their orders due to "impact from other generic products," even though providers were shipping more supplies than usual (more than 105%).

Another survey in March 2022 by Drug-Shortage.JP, a drug distribution database run by volunteers, showed 81% of 793 people – most of whom worked at clinics and pharmacies - had to change the way how they choose products to stock.

"I think, at first, there appeared the discussion in general that we have a shortage of generic drugs," said Sawai. He told Scrip the firm faced many demands from domestic associations of doctors and pharmacists to distribute "more products."

Although it made its best efforts to increase production by 10-20%, it was not enough to avoid harsh criticism from society regarding the trust and credibility of generic firms in general.

MULTIPLE FUTURE CONCERNS

Sawai also shared a number of concerns over the future of the Japanese generics industry. The first is the lack of "balance" in the market - he said he has seen some players order more drugs than usual in their haste to get stocks for pharmacies because of the quality crisis, thus driving the shortage.

The second is what he sees at the growing weight of responsibility on generic firms. Following the Japanese government's policy to increase the use of generics to cut national medical costs, the share of such products in the entire pharma market in the country reached 79.5% (in volume terms) between April 2021 and March 2022, according to a release from the Japan Generic Medicines Association (JGA) on 29 June.

However, some products are generating losses - according to Sawai, that applies to around 20% of its more than 800 products.

"Even though, we dare not stop producing those products – because providing generic drugs has been our social responsibility and duty. It's more than just a business," the executive emphasized.

The management challenges at Nichi-Iko - a ma-

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jor firm which provided 1,236 products as of April 2021 - are also driving Sawai's concerns. Nichi-Iko recently filed for a turnaround alternative dispute resolution procedure after posting a huge loss.

"In the near future, if a company like Nichi-Iko can no longer continue its business, who will fill the lost supply in the market? At least, it's too huge for Sawai alone," Sawai commented. (Also see "Nichi-Iko Aims To Regroup As It Enters Turnaround Process" - Generics Bulletin, 25 May, 2022.) (Also see "Nichi-Iko Offers Heartfelt Apology As It Forecasts Huge Annual Loss" - Generics Bulletin, 26 Nov, 2021.)

His third major concern is around the sustainability of Japan's generic market. While the Ukraine crisis and weaker Japanese yen have been pushing the price of fuels and materials in the country from the ground up, some generic firms may face another crisis under the current domestic drug pricing system, which keeps cutting prices of generics every year.

Sawai views support from the reimbursement system as even more crucial, given that many generic firms need to generate profit from their business in order to invest in areas such as IT systems and GMP-compliant manufacturing facilities.

PRICING REFORM SUGGESTIONS

On exactly how Japan's drug pricing system should be reformed, Sawai shared several ideas with Scrip. The first was to raise the "lowest drug price" (最低薬価), which was set at JPY10.1 ($0.074) per tablet/pill for products in frequent use or recognized as important and JPY5.9 per tablet/pill otherwise in February 2022.

"Among our products, around 200 of them are at the lowest price," observed Sawai. "As every material to produce a drug has a floor price, I think it is impossible to generate profit from the products with the current lowest price."

Another idea is to revert the pace of price revisions back to every two years, rather than annually, as many other pharma firms in Japan have suggested. Even if the country continues with industry-wide annual price cuts, Sawai proposed "the government should reconsider the level of its efficacy" on costs under the national health insurance system.

In 2021, the government started adding a "middle-year revision" (中間年改訂) between the existing regular official price revisions every two years, with the cuts being applied to more products than had been officially pre-announced. Sawai pointed out how the cuts – which in his view mostly hit generics – missed non-generic products with high prices, which form a large proportion of the government's healthcare costs.

> "I think this is the best and only chance for this country to seriously discuss the reformation of the [drug] pricing system."
>
> - Kenzo Sawai, President of Sawai Pharmaceuticals

"No matter how much the government squeezes the price out of generic drugs, its efficacy is limited [in decreasing government healthcare costs]," stated Sawai. He also suggested the system should start considering how much prices should cut on a yen currency base, not by percentage.

"[As a member of the generic industry] We had been lobbying for the reform of the current drug pricing system. But our voices had not been taken seriously because we had managed to make profits," he noted.

"Now that Japanese politicians are paying more attention to the pricing system, I think this is the best and only chance for this country to seriously discuss the reformation of the system. If we miss this one, the next one may never come."

(The second part of the interview will focus on Sawai's domestic and international business strategies.)

Lisa Takagi
Managing Editor, Japan

Japan Progresses 'Urgent Approval' System To Speed Drug Access

Japan is intending to revise existing pharma legislation to enable the urgent approval of new drugs with "assumed efficacy", with a maximum three-year period for confirmation, in cases of emergency need. The government will also ask companies to implement tighter safety monitoring and management of supply chains, with swift data disclosure required, as part of the planned changes.

Japan is planning to implement a system that would enable the urgent approval of new drugs without full confirmation of efficacy as long as this can be reasonably assumed from existing data and if the product is the only measure to tackle an urgent domestic health crisis.

The Committee on Health and Labour, Welfare of the House of Representatives decided on 15 April to pass a revision to the country's existing Pharmaceutical and Medical Device Act, which passed the House's main session on 19 April and was sent to House of Councillors for further discussion.

While the revision intends to provide more agility in the Japanese drug approval system, pharma companies would be expected to implement in parallel strict monitoring of the supply chain and quality, with swift information disclosure expected, especially in the reporting of any adverse events or health damage in patients.

As the government is aiming to enable broader data sharing around quality and supply controls as part of digital healthcare plans, further investment in systems by the pharma industry to enable both appears inevitable.

The decision in the House of Representatives was broadly supported by committee members including from the ruling Liberal Democratic Party and Komeito (a conservative political party), along with several opposition parties. The revision will be officially considered in the 208th National Congress, which will run until June.

MEETING NEEDS, WITH CONDITIONS

Unlike the current rapid conditional approval system in Japan (Toku-lei-sho-nin), which basically applies to drugs already approved overseas, the proposed new urgent approval system (Kinkyu-sho-nin) would apply across drugs, medical devices, vaccines and regenerative medicines. The biggest difference is that an approval would be possible if regulatory authorities can safely assume implied efficacy from interim clinical trial results - the current rapid approval system in Japan considers full confirmation of efficacy as mandatory.

"The urgent approval system is a measure to quickly provide Japanese citizens in need with medical care and the government must discuss the appropriate management setting in detail from now on," Prime Minister Fumio Kishida commented at the committee meeting.

COMPARISON OF RAPID APPROVAL SYSTEMS IN JAPAN

Japan is planning to enable urgent approval of drugs with assumed efficacy, although this has to be confirmed over a subsequent two-year (maximum three-year) period.

Name of Approval System (pronunciation in Japanese)	Normal Approval (Tsu-joh-sho-nin)	Special Rapid Approval (Toku-lei-sho-nin)	Urgent Approval (Kin-kyu-sho-nin)
Applicable to:	All drugs and vaccines	Drugs and vaccines already approved in foreign countries with equivalent system to Japan	Drugs and medical devices, vaccines, regenerative medicines
Purpose	To approve drugs with efficacy and safety confirmed through scientific evidence	To prevent urgent health crises, approve drugs already approved in foreign countries	To prevent urgent health crises, approve drugs with confirmed safety and assumed efficacy
Efficacy and Safety Measures	Efficacy: must be confirmed Safety: must be confirmed	Efficacy: must be confirmed Safety: must be confirmed	Efficacy: may be assumed Safety: must be confirmed

Source: Japan's Ministry of Health, Labour and Welfare

The exact review periods under the urgent approval system have not been disclosed and, as under the existing rapid approval system, confirmation processes for good manufacturing practices, quality and packaging are not mandatory. However, committee members insisted the government ask pharma firms to submit plans for manufacturing and product monitoring, as well as for the management of, and data disclosure, for risks and safety. Confirmation of safety remains mandatory.

The effective period for an urgent approval would be two years, with a one-time one-year extension granted if necessary. During that period, the further efficacy of the product must be confirmed and if this cannot be proven, the urgent approval will be cancelled immediately.

FURTHER INVESTMENT, STRICT MONITORING

The implementation of the urgent approval system, assuming final political approval, would seem set to benefit both the pharma industry and the Japanese government by enabling swifter decisions to deliver needed drugs to patients. Since the outbreak of COVID-19, the need for more rapid approvals has come under the public spotlight given the delayed delivery of vaccines and antivirals compared to the West.

However, the planned revision to legislation will also bring with it demands on the pharma industry for further investment in the monitoring of supply chains and quality/data management. There will also be an onus for the immediate disclosure to the government of information on any adverse events or health impact in patients or disruptions to supply.

Especially after the supply chain crisis for generic drugs started in 2021 after a series of GMP violations, the domestic pharma industry and the government has been discussing how better to maintain supplies of a variety of products of adequate safety and quality. (Also see "A Year's Struggle: How Japan Is Recovering Damaged Generic Supplies After Quality Violations" - Scrip, 12 Apr, 2022.)

The country has also been moving to develop digital healthcare services, including those related to personal health records and the enablement of digital prescriptions, which would be managed on a common platform connected to the nation's "My Number" personal ID system.

POLITICAL PASSAGE LIKELY?

The proposed revisions to Pharmaceutical and Medical Device Act will now be formally considered in the main conference of the House of Councillors and, if passed, the date of the formal implementation would be announced thereafter.

The revised law looks likely to pass the National Congress session ending in June given the consensus between several parties and support from almost all participants in the House of Representatives health and welfare committee, where the ruling party has a majority.

There has been some speculation that the urgent approval system may be applied to new drugs for SARS-CoV-2 such as Shionogi & Co. Ltd.'s oral antiviral S-217622, which was filed in Japan in February for rapid approval. While a preliminary decision was expected soon, there are signs the government is being cautious over the confirmation of efficacy. (Also see "Shionogi Files Oral COVID Antiviral In Japan, Vaccine Shows Phase III Promise" - Scrip, 10 Mar, 2022.)

Jung Won Shin
Senior Editor

What Is Slowing Industrialization Of Korean Digital Healthcare?

At a recent policy forum in Korea to discuss regulatory improvements, participants talked about the factors keeping the digital healthcare industry from taking off, despite ongoing efforts.

Although implementation of the Three Data Act in 2020 paved the way to shaping the regulation of digital healthcare in Korea, other legal and regulatory obstacles are still limiting the field from growing rapidly, particularly around the use of health and medical data, and reimbursement.

The Act referred to revisions to other existing legislation around the protection of personal information and information and communications networks, as well as credit-related information, the aim being to eliminate overlapping regulations and broaden the use of information by individuals and companies to foster new industries. It also established the concept of anonymous information to boost the use of such data.

At a recent Healthcare and Futures Forum organized by the Ministry of Health and Welfare and the Korea Health Industry Development Institute, participants discussed various policy issues and challenges seen to be slowing the larger-scale commercialization of digital therapeutics.

USE OF RESIDENT REGISTRATION NUMBERS

"We need separate laws to reinvigorate the digital healthcare or smart healthcare industry, and use of health and medical data," proposed the Korea Smart Healthcare Association's Moon-Gu Kim. "Even if we want to make use of personal information, this doesn't work in many cases because of certain minor legal obstacles."

This is seen in the country's health information highway, the so-called My Healthway system. Originally the plan was to use accumulated individual health information at medical and state-run institutions, and certain private bodies, through the platform by sending the data to entities that can make use of it to provide various new services.

Individuals can also receive their information using a health app from the National Health Insurance Service or Health Insurance Review & Assessment Service, and confirm their own treatment information via the apps of hospitals they visit. But if patients agree to confirm their information through healthcare service apps, these data cannot then be shared between the three platforms. According to the health ministry, this was largely because of Korea's resident registration number system.

When medical institutions use information from public institutions or private firms use data from medical or public institutions, personal user identification information must be used - which is the individual's resident registration number.

"Unless you are given the legal right to process the resident registration number, you can't use this under the Personal Data Protection Act," Kim explained. "Such realistic issues have limited the shape of the project from the original plans. Unless it is stated specifically in the law that the processing of a resident registration number is allowed or demanded, it can't be processed."

"Such a reality is unfortunate and I don't think this issue can be resolved at once. I think a separate law may be needed for the new ideas and projects to work properly."

REGULATORY HURDLES 'TOO HIGH'

Hyung-Wook Kim, chairman of the Korea Digital Health Industry Association, noted that healthcare firms in Korea have to generate revenues through the national health insurance system, but that no digital therapeutics have so far been added to the reimbursement list in the country.

"The market hasn't been formed properly, although the industry is making so much effort. The government has to take this into consideration. It is quite difficult, it takes much time and various steps to be added to the reimbursement list," Kim observed.

As regulatory hurdles in the approval stages are "too high," it will be difficult for innovative technologies such as digital therapeutics to blossom. As a result, he believes it necessary to consider whether the current process – going through a comprehensive evaluation process before allowing the market access - is actually the best option.

It would be worth considering measures such as allowing market entry first and then conducting evaluations later to bring forward innovative technology, as well as flexibly applying reimbursement and gathering complementary clinical data at a later date, he suggested.

For example, Germany enacted the Digital Healthcare Act in 2019, under which it established a temporary reimbursement system for digital therapeutics. These are eligible for reimbursement if they meet certain criteria including safety, quality and data security. If they pass the evaluation standards over a 12-month period, they will gain the legal right to reimbursement.

VOUCHER SYSTEM WORKABLE?

But given the serious financial deficit issues within South Korea's national health insurance scheme, it may be difficult to adopt a temporary reimbursement system akin to Germany's. One alternative would be a voucher service system, Kim suggested.

Such a voucher scheme is already being used by the health ministry and provincial governments to provide cost support for treatment and services for children with development disorders or mental disabilities, an area where many companies are developing digital therapeutics.

"In the short-term, this may intensify the national health insurance deficit issue, but in the longer term the benefit could be much larger by reinvigorating the industry," the association chairman said.

More broadly, the country is facing a rapidly aging society and so preventive healthcare is becoming increasingly important and along with it the use of wearable devices.

Examples include Ybrain, Inc.'s MINDD STIM, an "electroceutical" therapy for major depressive disorder, which received the first Ministry of Food and Drug Safety (MFDS) approval for such a device granted to a domestic firm. Along with an electroencephalogram device, SCAN, the MINDD platform helps with the processes of examination and analysis, treatment and result derivation. It can be prescribed without reimbursement in South Korea.

Meanwhile, a number of digital therapeutics are known to be progressing trials through trials in the country, although no approvals have been granted yet. For example, SK Biopharmaceuticals Co., Ltd is developing wearable devices to detect and predict epilepsy seizures to generate synergies with its anti-epileptic cenobamate.

This activity is putting a stronger spotlight on how the data generated by such approaches will be handled under legal frameworks.

LAWS 'COLLIDE WITH ONE ANOTHER'

"We have many laws [in Korea] related to health and medical data such as the Personal Information Protection Act, Bioethics and Safety Act and National Health Insurance Act. But these laws collide with one another. There is an issue of unclarity in the rules defining or consenting on health and medical data," Youn-Hee Choi, senior research fellow at Korea Institute for Industrial Economics and Trade, told the meeting.

Although there are guidelines to use this information, these are not working properly, she added. "What I am hearing from the industry is that there are still legal ambiguities. By using these data, the probability of violating laws hasn't been completely removed. I think this has to be clearly stated in each law."

Another issue is that the various laws state that such information can be used in research. But the "industrial" or commercial use of information also has to be specified in the relevant legislation; in addition, issues such as data ownership and transfer each have to be resolved, Choi noted.

The health industry is an area where technology innovation is taking place. "You may feel that the speed of technology innovation does not match that of regulatory improvement or advancement. I think there has to be a balance between the two," she added.

"We need to make more effort on the regulatory front so that it doesn't slow or weaken the will for technology innovation. We need to reach a consensus on what reasonable regulations are. This will refer to total regulatory cost and benefit - social cost stemming from the regulation and benefit stemming from improvement or advancement of regulation."

Such discussions will be the biggest policy task the country has to tackle, she predicted.

Lisa Takagi
Managing Editor, Japan

Integrating Data: Daiichi, Takeda Join Lifestyle Project To Inform R&D

The data collected from wearable devices for a year will provide lifecycle data to a much long-termed study with various health data. The study will not only contribute to drug discovery and personalized healthcare by the firms in near future, but also suggests bigger goals by Japan's healthcare industry.

Japanese research organization the Tohoku University Medical Megabank Organization (ToMMo), together with Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co. Ltd. and Japanese digital healthcare firm MICIN, have launched a joint research project that will use lifestyle data from around 2,000 people to inform a detailed analysis of how personal habits are related to health and disease.

The project - forming part of Japanese pharma's wider ongoing efforts to mover "beyond the pill" - will combine the collected data on parameters such as heart rate, activity level and sleep status from wearable devices with health data from other cohort research, Daiichi stating the aim is to contribute to innovative medical research "such as drug discovery aimed at achieving precision medicine and personalized healthcare." The firm also intends to expand and develop the framework of the study.

Meanwhile, information from a major domestic pharma industry association in the country also suggests plans for a similar but much bigger scheme involving academia and the Japanese government.

LIFESTYLE DATA TO BE INTEGRATED

The project, which started in March 2022, will end in 2025 and recruit up to 2,000 participants who have already joined the Health Surveillance Of The Brain And Psychological State Program with MRI run by ToMMo. The monitoring has been ministered in Miyagi prefecture since 2014 to enable preventive and personalized healthcare by following up how each participant's biomarkers are related to lifestyle-associated diseases and mental health issues, the latter being increasingly recognized in the area after the major Tohoku/Fukushima earthquake in 2011.

Although the current ToMMo scheme has collected various data including genetic factors, its

information on lifestyle habits is "based on the subjective responses of individual participants, which limits the ability to conduct objective and quantitative research." The new study with pharma industry involvement will run analyses on the collected data and use these for other long-term clinical studies and research.

Wataru Tasaki, general manager of Daiichi Sankyo's R&D division, commented that the firm expects the combined data "will greatly advance the early practical application of preventive and pre-emptive medical solutions."

Ceri Davies, head of neuroscience drug discovery a Takeda, commented the firm is hoping to develop new methods of using big data for the development of high-precision drugs and personalised healthcare tailored to the characteristics of patients.

JAPANESE PHARMA MOVING 'BEYOND THE PILL'

The broad consideration and adoption of digital and data-based healthcare approaches has been a key point within both Daiichi Sankyo and Takeda's recent mid-term strategies. While Daiichi has positioned data-driven drug discovery and the development of digital solutions as a key part of its current five-year business plan, Takeda has announced collaborations such as that with Mindstrong Health for developing digital biomarkers for mental health.

It is also developing a digital simulation tool for the treatment of Crohn's disease with PricewaterhouseCoopers, given its strategic interest in the gastrointestinal area through its blockbuster mainstay product Entyvio (vedolizumab) for inflammatory bowel disease.

These "going beyond the pill" initiatives are being widely adopted in the Japanese pharmaceutical industry and recommended by the Japan Pharmaceutical Manufacturers Association (JPMA). In April 2022, Eisai Co., Ltd. announced the acquisition of digital healthcare solution provider Arteryex to enhance its digital service platform. (Also see "Arteryex Acquisition To Enhance Eisai's Digital Strategy" - Scrip, 14 Apr, 2022.)

Astellas Pharma, Inc. has also highlighted a wide range of digital strategies, from R&D to decentralized trials. (Also see "Astellas Positions Patients At Center Of Digital Push" - Scrip, 26 Jan, 2022.)

For industry groups like the JPMA, enabling more cost-efficient and high-quality drug discovery using digital technologies is seen as one of the most important goals for the entire domestic pharma sector. The association, which has been supporting ToMMo's cohort study since 2020 along with the Japan Agency for Medical Research and Development (AMED), has strongly suggested the construction of a healthcare data platform and its safe application to drug discovery projects.

JPMA'S DIGITAL FUTURE PRIORITIES

Further interesting context to the new study announced by Daiichi Sankyo and Takeda is that it appears to echo the JPMA's suggestions on digital healthcare measures released last year. In March 2021, the association published a document on policy recommendations for the pharma industry.

In this, the JPMA highlighted ToMMo's cohort studies as "useful for drug discovery," while also recommending five other major government-led measures for the next 10 years to enrich data and outcomes (see below). The first of these seems to align well with the Daiichi Sankyo/Takeda initiative just announced.

1. To collect detailed data on lifestyle habits using wearable devices. Pharmaceutical firms should contribute to this measure by planning and funding joint studies.
2. To analyse the genomes of around 100,000 people using public funding.
3. To create an environment for the integrated analysis of data from biobanks including ToMMo by leading collaboration between biobanks
4. To create a data platform system which enables the use of data from ToMMo's studies by collaborating with medical institutions in Miyagi and Iwate prefectures.
5. To train and retain human resources to support joint studies on data analysis and administration.

Anju Ghangurde
Executive Editor, APAC

The Old Order Changeth: Women CEOs at Foreign Firms In India Chart New Course

Foreign firms including Merck KGaA, Boehringer Ingelheim, Takeda and Sanofi's vaccines business are being led by women in India, a fiercely competitive, largely out-of-pocket market. There's a lot riding on these female leaders as they seek to drive business growth and potentially change the paradigm around the gender gap in pharma at the top.

More women are moving into the corner office in pharma in India, with Merck Specialities Pvt. Ltd, the healthcare business of Merck KGaA emerging as the latest foreign firm that will be steered by a female executive in the country.

Company long-timer Pratima Reddy was appointed as managing director of Merck Specialities effective 1 August, emerging as the first woman CEO for the group's healthcare business in India.

Reddy's elevation comes after a relatively "rough year" amid the COVID-19 pandemic, with the company deciding on a strategy "refresh" to sharpen the focus of its teams and drive sustainable growth across its franchises.

"Four global strategic priorities underpin our refreshed approach: growing our core business, maximizing launches, leveraging digital to drive growth and harnessing the power of our people and culture," Reddy told Scrip.

Last year Merck launched in India its advanced infertility treatment Pergoveris Pen, a ready-to-use combination treatment option for women with severe follicle-stimulating hormone and luteinizing hormone deficiency, as also the Pfizer Inc.-partnered checkpoint inhibitor Bavencio (avelumab).

Within the fertility portfolio, Merck was also working in India to develop a new "digital health ecosystem" that can help patients "feel more involved, and better taken care of, throughout their fertility journey," Reddy's predecessor Anandram Narasimhan had told Scrip at the time. (Also see "Merck KGaA Stepping Up In India, Eyes On Bavencio Trajectory" - Scrip, 6 Sep, 2021.) (Also see "Interview: German Merck Set For Big "Leap" In India" - Scrip, 26 Sep, 2016.)

INDIA

ON SUSTAINING ONCOLOGY MOMENTUM, PRODUCT LAUNCH PLANS

Merck's Pratima Reddy: The Indian market focus is slowly leaning more towards other sectors, and one such extension is oncology.

With multiple lifestyle changes, the cancer diagnosis rate in the country today is exceptionally high compared to previous years' data. With an increased cancer burden on health systems and high unmet medical needs, Asia Pacific sees considerably high cancer mortality rates.

As early innovators in immuno-oncology and precision medicine, Merck continues to take a biology-focused approach as we develop our portfolio and pipeline.

Our newest drug Bavencio launched last year in our oncology therapy unit, is already making a difference in patients' lives. Bavencio is co-marketed by Merck and Pfizer in India and globally. We are building conviction through in-market activities - global expert meets, peer-to-peer meets reached an all-time high this year (engaging more than 2,000 doctors). With the increasing unmet need of Indian cancer patients, the launch of Bavencio is a beacon of hope for many patients in India.

This gives us the confidence to look at indications that require globally successful therapies. We are always looking for opportunities to bring global brands to India. We focus on enhancing access to our portfolio of medicines across the country. With a renewed mission post-COVID, we are now designed to amplify each therapy area's strengths. There are ongoing conversations around bringing some immunotherapy drugs to India because there is such a need that stands out in the country.

Reddy indicated that several organizational changes and a new operating model to support the life science business sector's long-term growth strategy better serve its customers' evolving needs are being implemented.

"Science and technology are advancing at an unprecedented speed, and with that are the needs and expectations of our customers worldwide. A suitable operating model will accelerate the ability to provide customers with the best products and services," she added. Reddy had in a previous stint led the turnaround of the oncology business in the country by demonstrating the opportunity to drive strong growth via focused access strategies.

Within the German group, Reddy's new role perhaps isn't viewed as too unusual. Merck KGaA has been an industry outlier of sorts and is led by CEO Belen Garijo, who is also chair of the executive board. At the time of her moving to the helm last year, Garijo was reported as being the only solo woman chief of a company that's a constituent of the DAX, the German blue chip stock market index. Jennifer Morgan, co-CEO of software company SAP was the other woman chief, but had a short stint at the helm. (Also see "Changing Of The Guard At Merck KGaA With Garijo Succeeding Oschmann As CEO" - Scrip, 29 Sep, 2020.) Garijo is among the few female pharma CEOs at big pharma alongside GSK plc's Emma Walmsley.

OTHER WOMEN LEADERS IN INDIA

Back in India, though, Reddy isn't the only female chief to helm a foreign biopharma firm. German peer Boehringer Ingelheim, Takeda. and Sanofi's vaccines business all have women at the helm. Several Indian pharma firms too have women leaders who have proved their mettle over the years. (See chart - not an exhaustive list.)

WOMEN AT PHARMA'S HELM IN INDIA

Company	Executive	Leadership Role
Merck Specialties	Pratima Reddy	Managing Director
Boehringer Ingelheim	Vani Manja	Country Managing Director for India
Takeda	Serina Fischer	General Manager India
Sanofi	Annapurna Das	Head of Vaccines, Asia
Sanofi India	Preeti Futnani	General Manager – Vaccines*
Roche India	Lara Bezerra	Managing Director#
Cipla	Samina Hamied	Executive Vice Chairperson
Lupin	Vinita Gupta	CEO
Biocon	Kiran Mazumdar-Shaw	Executive Chairperson
Indoco Remedies	Aditi Kare Panandikar	Managing Director
Piramal Group	Swati Piramal	Vice-Chairperson
Piramal Pharma/ Piramal Enterprises	Nandini Piramal	Chairperson/ Executive Director

**Futnani succeeded Annapurna Das, who was elevated as Sanofi's Head of Vaccines, Asia #Bezerra led Roche India from Nov 2017 to 1 Dec 2019; V Simpson Emmanuel now heads Roche Pharma India as CEO & MD*

Boehringer Ingelheim's country managing director for India, Vani Manja, who took over the reins amid pandemic turbulence in 2021, had to hit the road running, steering the group's growth efforts while fending off patent challenges to Jardiance (empagliflozin) and Trajenta (linagliptin) alongside. (Also see "Boehringer Ingelheim Primes For Top Five Multinational Slot In India" - Scrip, 28 Mar, 2021.)

Takeda's general manager (India), Serina Fischer, too likely has a lot on her plate as she strives to build momentum with a mix of new products like the gut-selective biologic, vedolizumab (available as Entyvio internationally) as also drawing on the ex-Shire PLC range of therapies in the largely out-of-pocket Indian market. (Also see "Takeda Expands Hemophilia Play In India But Hemlibra Has Made Inroads" - Scrip, 20 Jun, 2022.) (Also see "Takeda Introduces Vedolizumab In India Amid Signs Of Gear Shift" - Scrip, 13 Jul, 2020.)

2022 also saw Sanofi transition Preeti Futnani, its franchise head for Dupixent dermatology in the Greater Gulf MCO (a cluster of six countries including Saudi Arabia, UAE, and Kuwait), as general manager, vaccines, in India.

Futnani, who moved into the top India position in June, began her tenure in Sanofi over six years ago in Specialty Care Gulf, after stints of increasing responsibility at Novartis in marketing and commercial operations across Switzerland, the UK, and India. She succeeded another female leader, Annapurna Das, who was elevated to Head of Vaccines, Asia, at Sanofi.

DIVERSITY IN THE BIOTECH INDUSTRY

Ideally, women moving up to helm pharma in India or elsewhere shouldn't really make headlines – talent should not to be determined by gender, color, race or ethnic background.

But biopharma as a whole, still has considerable ground to cover to improve gender representation and ensure that women have a truly level playing field when it comes to top jobs. The gender pay gap is another key area that warrants more efforts across the board. (Also see "Mind The Gap: UK Gender Pay Report Is Time Bomb For Pharma" - Pink Sheet, 12 Mar, 2018.)

For instance, BIO's third annual report "Measuring Diversity in the Biotech Industry: Tracking Progress in Small and Large Companies" noted that gender representation of employees in the latest sample achieved near parity — companies reported that 49% of their total employees are women versus 51% men. (Also see "BIO 2022 Notebook: Future Directions For R&D" - Scrip, 16 Jun, 2022.) (Also see "Gender Diversity In Pharma: Caught Between Desire And Reality" - In Vivo, 11 Dec, 2019.)

However, the representation of women continued to decrease at higher levels of an organization — only 34% of executive teams and 20% of CEOs were reported to be women, the findings from the voluntary survey of 99 BIO member companies from November 2021 to January 2022 indicated. In the 2020 sample, closer to one in four CEOs (23%) were women.

The report also affirmed that a key policy that continually emerges as vital to diversity, equity and inclusion progress is pay equity; undertaking a pay equity analysis helps "correct for past bias in compensation decisions", as pay gaps often show up for women and employees who are not white, it noted. In terms of actually moving to action, 77% of large companies and 44% of small companies had taken steps to ensure pay equity, the report noted.

But most large companies now appear to be making earnest efforts to bridge the gender gap. In India, multinational companies such as GlaxoSmithKline Pharmaceuticals Ltd. have made notable strides in nurturing women leaders.

GSK told Scrip that the pandemic allowed it to "pause for purpose" and re-imagine the charter to draft a roadmap for women in India.

The company's Women's Leadership Initiative Employee Resource Group, now in its new avatar, plays a pivotal role to strengthen inclusive culture and increase leadership accountability by focusing on three pillars: culture, capability and careers. "Through KPI-led periodic reviews, leadership-led interventions and a rapid feedback loop, the team aspires to elevate the experience of women at GSK," it explained.

GSK's Women's Leadership Initiative (WLI), which is chaired by Dr Rashmi Hegde, executive vice president – medical affairs, is working to amplify the firm's efforts to be a "disruptive innovator, trustworthy employer and happier workplace" through strengthening an inclusive culture and increased leadership accountability; 66% of the WLI team is represented by women across all levels and functions.

Some of the key milestones achieved over these years include the elevation of two India women leadership team members to critical regional and global roles in GSK, while current gender representation stands at 12% with a slight increase observed amongst commercial teams in the Indian arm of the UK multinational.

More widely, 21% of the India leadership team in GSK Pharmaceuticals are women, while in senior manager and above positions 23% are women; 18% of the new hires in the company are women (year-to-date July 2022).

On whether the WLI also looks into gender pay gap issues, GSK said that human resources

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team does this exercise annually to analyze and addresses any gaps with support from the chief human resources officer and business leaders. "The consolidated outcome is reviewed at the leadership team level."

Indian firms too are acting in the area and some have laid out ambitious plans. For instance Dr. Reddy's Laboratories Ltd., the only Indian pharma company to be featured on the Bloomberg Gender-Equality Index 2022, aims to have at least 35% women in senior leadership (3X from current levels) by 2030 and achieve gender parity for the organization by 2035. Of the firm's 20,122 permanent employees, 2,327 are currently women.

WOMEN LEADERS DEMONSTRATE GAME-CHANGING IDEAS

While most of the gender partity plans are work in progress, the arrival of leaders like Reddy, Manja, Fischer, Futnani and Das reinforce that "the times they are a-changin", if one were to borrow from legendary folk singer and writer Bob Dylan's iconic title track.

Merck's Reddy stated that women today are altering "traditional practices" by introducing a diverse approach to face challenges head-on and promote growth and as a result, they are proving to be the "game changers" in reinventing leadership globally.

"Today I see my peers demonstrating game-changing ideas and services in some of India's top pharma and healthcare companies," she told Scrip.

She encourages women aspiring to move up the corporate ladder to take risks by focusing on their strengths, "staying their authentic self" and also rallying to create an impact that would matter to the community and future generations.

"We will hopefully see more women emerge in this sector and make a difference in the lives of millions," she declared.

BI's Manja had similarly noted that the gender gap issue is not just an India or pharma challenge but a truly global one and while progress had been made in the last couple of decades, it is "woefully short" of the balance that is needed to harness the full potential of talented women in the workforce and in society.

"Much work needs to be done and this is a conversation that we need to keep going," she told Scrip in an interview in October last year. (Also see "B-Ingelheim India Chief On Strategy, Jardiance Challenge, Gender Balance In Pharma" - Scrip, 27 Oct, 2021.)

Manja urged women leaders to be their best advocate and not limit possibilities because of "how others may perceive you".

"Don't ever sell yourself short. Seek, take and own your seat at the table with confidence, not apology," she underscored at the time.

While these words of advise augur well and several firms are making concerted efforts to increase the gender diversity of senior ranks, COVID-19 has thrown up new challenges in retaining women in the workforce as they struggle to balance work/life arrangements and shoulder additional responsibilities in the new normal way of life.

A McKinsey study indicated that pre-COVID-19, women in corporate America had slowly been making some progress in the workplace across industries. Between January 2015 and December 2019, the number of women in senior-vice-president positions rose from 23 to 28 percent, and in the C-suite from 17 to 21 percent.

But the pandemic has dealt a huge blow with one in four women considering exiting the workforce or downshifting their careers versus one in five men. "While all women have been impacted, three major groups have experienced some of the largest challenges: working mothers, women in senior management positions, and Black women," McKinsey said in an article last year.

Hopefully as the pandemic recedes, more women will opt to rejoin the workforce and progress their careers, traditional and new barriers notwithstanding.

INDIA

India Physician Conduct Rules Want Them Off Pharma-Sponsored Symposia

Anju Ghangurde
Executive Editor, APAC

Wider-ranging new draft rules suggest that physicians in India should not engage in educational activity sponsored by pharma and urges them to declare financial earnings and benefits received from industry via an affidavit. The Pink Sheet discusses with industry experts some of the nuances and seeming loopholes in the rules, currently in self-regulatory mode but with penalties proposed for violation.

India's new rules pertaining to the professional conduct of Registered Medical Practitioners (RMPs) puts a question mark on the participation of physicians in pharma-sponsored conferences and urges them to come clean about their relationship with industry. The wide-ranging rules cover a gamut of areas including guidelines on social media conduct of RMPs and telemedicine, and also prohibits endorsement of products.

The National Medical Commission (NMC) Registered Medical Practitioner (Professional Conduct) Regulations, 2022, currently in draft form, specify that RMPs should not be involved in any third-party educational activity like continuing professional development (CPD) programs, seminars, workshops, symposia or conferences which involve "direct or indirect sponsorships" from pharmaceutical companies or the allied health sector.

The rules maintain that physicians should be "aware of the conflict of interest situations that may arise" and that the nature of these relationships should be in the public domain and not contravene any law, rule or regulation in force.

"An RMP himself or as part of any society, organization, association, trust, etc. should be transparent regarding the relationship with the pharmaceutical and allied health sector industry," state the rules, which are open for comments until 22 June.

DELINKING PHARMA FROM CONFERENCES UNREALISTIC?

While the transparency requirement is clearly the way forward, industry experts maintain that keeping pharma out of the medical conferences equation is impractical.

Ranjit Shahani, ex-vice chairman and managing director of Novartis India Ltd., said that "reasonable" efforts are made on RMP capacity-building, awareness and educational initiatives, and also highlighted the rapid pace at which innovations happened over the past two years itself – mainly attributed to COVID-19.

"Therefore, restricting RMPs from being involved in educational seminars, symposia, CPDs etc. will significantly impact the ecosystem. Also, how do you expect these programs to run/sustain without the support of pharmaceutical companies or allied sectors?" Shahani said in comments to the Pink Sheet.

The industry veteran noted that India doesn't really have independent, "financially well-backed-up" associations, R&D set-ups or academia to sponsor such programs.

"It's unrealistic to delink participation of pharma companies/ allied sectors from such programs. In fact, it's the sector's responsibility to operate such programs on a larger scale and RMPs be involved in these activities," he declared.

Others mirrored similar views, but also pointed out that the NMC guidelines are essentially meant to be "self-regulatory and strictly ethical" in nature.

"It is quite difficult to believe that medical conferences and meetings will happen without sponsorship from pharma or allied health sector. This will mean that the associations will have to raise the money from their members," said Salil Kallianpur, a former executive vice-president at GlaxoSmithKline plc in India.

But Kallianpur believes that the fact the guidelines are not meant to be legal - and therefore not law and cannot be binding - provides a "neat little loophole" that can be used.

"I hate to be pessimistic but this is unlikely to happen in the near term as the transactional nature of relationship between pharma and doctors is quite strongly embedded," Kallianpur, who now runs a digital health consultancy, told the Pink Sheet. The National Medical Council's code of ethics is framed as a self-regulatory set of guidelines reflecting professional and social expectations.

Probably keeping that in mind, the guidelines in parallel recommend transparency and a declaration of lack of conflict of interest by physicians "as an option", the executive noted, adding that it is not a completely new section and has existed since the Indian Medical Council Regulations of 2002, which was then hailed as India's "Sunshine Act."

SOCIAL MEDIA CONDUCT

The National Medical Commission Registered Medical Practitioner (Professional Conduct) Regulations, 2022 also provide guidelines on social media dos and don'ts.

Among a range of suggestions, the guidelines say that while RMPs can provide information and announcements on social media, this should be factual and such that it can be verified. The information should not be "misleading or deceptive, nor should it exploit the patient's vulnerability or lack of knowledge."

In what's probably a reflection of the far-reaching impact and tactics on social media, the guidelines also underscore that RMPs should not directly or indirectly purchase "likes, followers" or pay money so that search algorithms "lead to their name being listed at the top" or registering on software programs (apps) that charge fees for higher rating or soliciting patients.

Physicians also should not share patient testimonials or recommendations/reviews/endorsements on social media, the regulations add. RMPs also need to distinguish between social media and telemedicine consultation, the rules specified, setting out a range of norms for the practice of telemedicine in India.

NO GIFTS, TRAVEL FACILITIES

The draft rules also touch on the infamous gifts and hospitality component of the physician-pharma relationship. It specifies that RMPs and their families should not receive "gifts, travel facilities, hospitality, cash or monetary grants, consultancy fee or honorariums, or access to entertainment or recreation" from pharmaceutical companies, commercial healthcare establishments, medical device companies or corporate hospitals.

However, the norms specify that this does not include "salaries and benefits" that RMPs may receive as "employees" of these organizations – again seemingly a window for the consultant physician or then the medical associate role in pharma, which potentially can then be assumed to be beyond the purview of the rules.

Kallianpur believes that this is definitely a loophole, where a healthcare professional (HCP) may be "hired" as an advisor or consultant and a payment may be made by pharma or the allied health sector at "fair market value."

Ex-Novartis India chief Shahani maintained that if RMPs are involved in scaling up capacity building/ educational efforts, then there should not be any restriction on "adequate" compensation.

"There could be some fair value guidelines which can be designed to ensure that companies or RMPs are not using such contracts to unfair advantage," he suggested.

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Industry veteran and president and CEO of Danssen Consulting, Dr Ajit Dangi, noted that, as is seen in most pharma companies in India and in developed countries, it is a common practice to have doctors and disease specialists in a company's full-time employment as a part of its "medico marketing" team.

"One presumes that such professionals are exempted from these ethics guidelines, although appointing part-time consultants to play an advisory role is a grey area and needs to be specifically defined," Dangi, a former president and executive director of Johnson & Johnson in India, told the Pink Sheet.

Dangi also underscored that much depends on the "intent" when it comes to gifts, travel facilities and monetary grants to RMPs by pharma. For instance, if a KOL (key opinion leader) is invited to present a research paper on a particular new drug at a conference, as long as they present the data in an "objective manner" without mentioning the brand name and are compensated "modestly" for this professional service, "there should not be any problem."

"One way of solving this problem is to give funding to the conference organizers and the organizing committee decides how to allocate the funds equitably to the presenters," the executive suggested.

However, it's unclear if such funding may be construed as indirect support, some industry observers said.

AFFIDAVIT ON RMPS' FINANCIAL EARNINGS FROM PHARMA

Strikingly, the rules also suggest that RMPs may be required to file an affidavit regarding their financial earnings and benefits received in the past five past years from pharmaceutical companies or the allied health sector.

While it's unlikely that the medical community will, in totality, be keen to fall in line with these suggestions, Shahani said that the norms are indeed a fair expectation.

"If rules regarding participation, engagement and consulting contracts are clear – then RMPs should be encouraged to be transparent regarding their financial earnings. Issue creeps in when there are restrictions on everything and people find alternatives to bend those rules."

For instance, the seasoned executive noted that if an RMP is engaged with a pharma company for a patient registry program or supports a CME (continuing medical education)/educational activity for which they are being trained and can then be compensated for training a larger network of RMPs, "then what is there to hide?"

With the "right rules," expectations of transparency can be maintained and this will not be a "big operational hazard," he declared.

Kallianpur said that the affidavit requirement is perhaps the most important part of the guidelines from an implementation point of view and provided a distinct dimension on a potential snag.

He explained that the whole idea is about avoiding tax evasion and as long as doctors declare "what they receive from pharma and others, as taxable income [as proposed in the Finance Bill]," the government should have no problem with them.

"Filing an affidavit [to anyone other than tax authorities] will probably be seen as an additional activity and unless there is a sound reason in doing so, complying to this could be a problem," he added.

Dangi similarly believes the affidavit requirement for RMPs is a classic case of "over regulation" and is not only unlikely to pass muster with the medical community but is also "oblivious of the ground realities."

ENDORSEMENT PROHIBITION

Another part of the draft regulations calls for the prohibition of endorsement of "the product or a person" by a RMP, raising questions on whether this could imply that physicians aren't supposed to be talking about the benefits of a particular new drug/molecule.

Specifically, the rules suggest that RMPs shouldn't provide any "approval, recommendation, endorsement, certificate, report, or statement concerning any drug, medicine, nostrum remedy, surgical, or therapeutic article, apparatus or appliance or any commercial product or article with respect of any property, quality or use thereof or any test, demonstration or trial thereof, for use in connection with his name, signature, or photograph in any form or manner of advertising through any mode."

Nor should the RMP "boast of cases, operations, cures or remedies or permit the publication of report thereof through any mode."

Shahani believes such prohibition could pose a "risk" to the industry and the overall healthcare ecosystem in general. "The issue is on drawing lines and understanding how 'recommendation' is different from 'promotion/ endorsement,' he commented.

He explained that most R&D-led companies do significant clinical, real-world evidence studies for their molecules and these are led by KOLs and physicians to understand safety and efficacy profiles - these are not only for new drugs but also mature molecules/fixed-dose combinations to understand different aspects.

"Physicians, RMPs should have the flexibility of analyzing such outcomes and publish them as part of research work undertaken by them, which is validated by external entities," he asserted.

Such outcomes become part of broader practice network and help RMPs drive awareness-building across larger community of RMPs, practice improvement based on clinical evidence amongst different patient profiles and also share clinical case studies which form the basis of CME.

"Most patented drugs were successful in India over the past decade because companies and HCPs, KOLs put in effort and understand clinical cases to drive wider adoption amongst a broader set of generalist physicians," the former Novartis India head pointed out.

Ex-GSK executive Kallianpur, however, said that the RMP guidelines could essentially mean that RMPs do not offer a testimonial like they do in a local advert for Sensodyne toothpaste - hence GSK clarifies that the said HCP practises in the UK.

"In India, doctors stay away from such endorsements anyway. I do not think that it will change how pharma engages with them because doctors can still talk about the benefits of a molecule as witnessed in their clinical practice. The sharing with other doctors via a CME or in a medical conference is done as a discussion about how the doctor treated a particular patient," he observed.

He believes that as long as doctors stick to discussing the "disease, the molecule, the science and the general role in therapy and treatment," they will not violate the NMC guidelines. Other industry experts said the guidelines need to clarify or come up with a kind of addendum on some of the nuances to avoid confusion.

DISCIPLINARY ACTION

Breach of the guidelines could attract disciplinary action, which is structured into levels ranging from "reformation" at level one, all the way to debarring a physician permanently from practice under level 5, if they have committed wilful/intentional harm and an unlawful, prohibited action.

Levels 2, 3 and 4 could entail reformation or suspension of license to practice for specified periods.

The Ethics and Medical Registration Board has the power to draft guidelines on penalties for misconduct, including a monetary penalty among others, details in the rules suggest.

NEEDS WIDER CONSENSUS?

Meanwhile, Ex-Novartis India chief Shahani underscored that the new guidelines still require wider consensus amongst all stakeholder groups – including pharma companies and allied healthcare sectors - for them to be effective in implementation.

"In its current form, it restricts capability and awareness-building initiatives for RMPs/HCPs, platforms and forums of how the ecosystem can work more effectively; and therefore does not solve far larger issues around accessibility of appropriate treatment," he asserted.

Parts of the guideline have also been mentioned in other rules such as the Uniform Code of Pharmaceutical Marketing Practices (UCPMP) guidelines that were released by the India's Department of Pharmaceuticals in 2015 and is currently voluntary in nature. (Also see "AdvaMed Launches Ethics Code To Meet 'Business And Market Realities' In India" - Medtech Insight, 28 Oct, 2021.)

Jung Won Shin
Senior Editor

The Race Is On. When Will Korea Have Its Own Approved Gene Therapy?

Scrip takes a look at the landscape of the South Korean gene and cell therapy sector, which is under the spotlight with the implementation of a new cutting-edge biologics law.

While global pharma firms are rolling out advanced gene and cell therapies, as well as aggressively making R&D investments in the space to grab the leading position in the burgeoning market, South Korea is still seen as lagging behind in the development of these innovative modalities such as CAR-T cell therapies.

According to the recent Cell, Gene & RNA Therapy Landscape report from Informa Pharma Intelligence and the American Society of Gene + Cell Therapy, a total of 89 gene, cell and RNA therapies had been approved in the global market as of the fourth quarter of 2021. Non-genetically modified cell therapies accounted for the majority with 55 approvals, followed by 19 for gene therapies, including genetically-modified cell therapies, and 15 for RNA therapies.

Moreover, a substantial 3,483 therapies are in development, ranging from preclinical through to pre-registration, among which 1,941 gene therapies (55% of the total, including genetically-modified cell therapies such as CAR-Ts), are in development. In the fourth quarter of last year alone, Phase III studies for gene therapies increased by 10% from the previous quarter, the report shows.

In South Korea, more approvals are likely to follow for global companies' gene therapies in the wake of the local Kymriah (tisagenlecleucel) and Zolgensma (onasemnogene abeparvovec) green lights for these Novartis AG products last year under the new regenerative medicine law. Even so, the majority of cutting-edge biologics such as CAR-Ts and RNA therapeutics under development by Korean firms remain in the early research stages.

At present, developers from the country are progressing the development of 117 cell and gene therapies, but the majority are stem cell or non-genetically modified cell therapies, observed a recent report issued by Korea Health Industry Development Institute (KHIDI). (Also see "Cutting-Edge Biologics Approvals, Trials Pick Up In Korea After New Law" - Pink Sheet, 9 Dec, 2021.)

KOREAN GENE THERAPY SETBACKS

Following the cancellation of the local approval of Kolon Life Science, Inc.'s allogeneic cell and gene therapy for knee osteoarthritis Invossa (TissueGene-C; tonogenchoncel-L) a few years earlier, there don't seem to be any further near-term approvals of cutting-edge gene therapies on the horizon for domestic firms.

In fact, multiple Korean companies progressing late-phase gene therapies have faced setbacks over the past few years. While they have managed to slowly move forward with development in the US or other parts of the world, it remains to be seen whether they can generate positive results from their trials and move on to approval and commercialization.

In 2019, Korea's Ministry of Food and Drug Safety canceled its approval of Invossa after it concluded Kolon Life submitted false data to support the approval. The firm subsequently filed an administrative lawsuit to withdraw and suspend the administrative measures and the candidate resumed a US Phase III study for knee osteoarthritis (OA) and also begun a Phase II program for hip OA. (Also see "A Glimpse Of Light For Kolon As US Invossa Trials To Resume" - Scrip, 14 Apr, 2020.)

Other Korean firms with late-stage gene therapy pipeline assets have faced speed bumps. Oncolytic virus firm SillaJen, Inc., which found a new owner in 2021 amid illegal activities by some executives, is still suspended from stock trading. The company suffered early stoppage of a global Phase III trial in liver cancer for its oncolytic virus therapy Pexa-Vec (pexastimogene devacirepvec), although it is progressing key clinical trials as well as other R&D and management activities normally.

Helixmith Co., Ltd., meanwhile, has received the US Food and Drug Administration approval to use a new formulation of Engensis (VM202) in an upcoming Phase III trial for diabetic peripheral neuropathy, a move that may bring the company closer to commercialization of the plasmid DNA therapeutic, its lead pipeline asset.

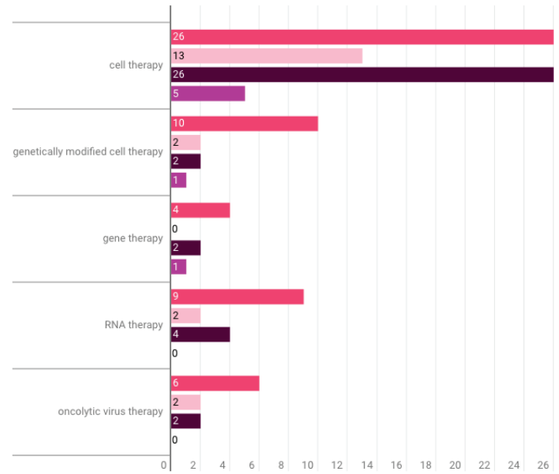
After failing to meet the primary endpoint in what it termed a Phase III-1 trial, Helixmith said Engensis had shown significant and clinically meaningful pain reduction versus placebo in an extended Phase III-1b study for the indication and decided to push ahead with additional Phase III plans. (Also see "Helixmith's Plasmid DNA Therapeutic Moves Forward With New Formulation" - Scrip, 14 Mar, 2022.)

OVERSEAS COLLABORATIONS, R&D INVESTMENT NEEDED

As it is difficult for individual companies to develop technology using only in-house capabilities in a

Korean Gene And Cell Therapy Landscape

Gene and cell therapy pipelines held by Korean firms



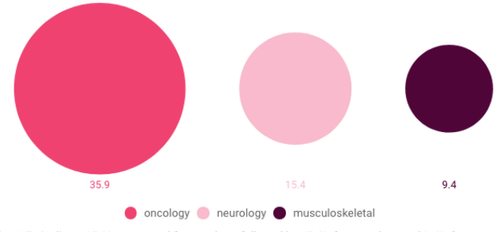
Among the 117 cell and gene therapy pipelines held by Korean firms, cell therapies accounted for the biggest portion at 57.8%, followed by 13.2% for genetically modified cell therapies, 12.4% for RNA therapies, 8.3% for oncolytic virus therapies and 5.8% for gene therapies.

Cell therapies accounted for majority of Phase III pipelines
Pharmicell (Cellgram-liver), Anterogen (ALLO-ASC), Kangstem Biotech (Furestem-AD), Nature Cell/R Bio (JointStem)

Only one genetically modified cell therapy undergoing a Phase III
Kolon Life/Kolon TissueGene (TissueGene-C)

Only one gene therapy undergoing a Phase III
Helixmith (Engensis)

No RNA therapeutics or oncolytic virus therapies undergoing Phase III
None



Of the 117 pipelines, 35.9% accounted for oncology, followed by 15.4% for neurology and 9.4% for musculoskeletal system.

Korean Companies' Cell And Gene Therapy Pipeline Acquisition Method

		cell	RNA	gene	genetically modified cell	oncolytic virus	TOTAL
M&A	domestic	-	-	-	-	-	
	foreign	-	-	-	-	1	1
in-licensing	domestic	4	2	1	-	-	7
	foreign	5	-	-	-	-	5
co-research	domestic	-	2	-	-	-	2
	foreign	2	1	-	-	-	3
proprietary technology		59	10	6	15	9	99
TOTAL		70	15	7	15	10	117

(source: KHIDI report)

short period of time, and as global pharmas are increasingly licensing in key technologies, it appears there's an opportunity for Korean firms to make bold R&D investments and aggressively seek partnerships and even mergers and acquisitions with foreign companies, which have core technologies and clinical know-how.

So far, the Korean industry has been more focused on collaborations with domestic firms rather than cross border tie-ups. In addition, the government should also come up with policies to support the industry's globalization moves and collaborative research projects to further upgrade the international competitiveness of the country's gene and cell therapy capabilities, the KHIDI has suggested.

One recent successful cross-border alliance in the sector was between GC Cell and Artiva Biotherapeutics, Inc., which subsequently led to a large out-licensing agreement with Merck & Co., Inc. for preclinical stage chimeric antigen receptor-natural killer cell therapies. (Also see "Merck & Co. Looks To Artiva's Off-The-Shelf Cell Therapy Technologies" - Scrip, 28 Jan, 2021.)

LARGE FIRMS MORE FOCUSED ON MANUFACTURING

Along with the global acceleration in the development of cell and gene therapies, contract development and manufacturing market has been growing rapidly, as half or more manufacturing of cell and gene therapies is known to be outsourced. Unlike smaller Korean bioventures, which largely focus on development activities, larger Korean firms, particularly conglomerates such as SK Group and Samsung Group, are also engaged in manufacturing.

According to a recent report by the Korea Biotechnology Industry Organization, global firms are seeking to grab leadership in the rapidly growing CDMO market and Korean companies are likely to have to compete fiercely, particularly Japanese companies which are actively seeking M&As and in-licensing of technologies to obtain pipeline assets.

Through affiliate SK Inc., SK Group has been the most active in expanding into manufacturing by acquiring US-based the Center for Breakthrough Medicines early this year, only nine months after it bought Yposkesi in France.

Samsung BioLogics, an affiliate of Samsung Group, is also planning to expand its antibody therapeutic-focused CMO business portfolio to the manufacturing of mRNA, plasmid DNA and viral vector-based gene and cell therapies, as well as next-generation vaccines. With a goal to receive cGMP certification in the second quarter, it is building mRNA-based API manufacturing facilities within its existing plants.

CJ Group's CJ CheilJedang Corp., meanwhile, has also diversified into manufacturing by acquiring a majority stake in Netherlands's Batavia Biopharma B.V. late last year. Smaller Korean companies such as GC Cell, ST Pharm, Daewoong Pharmaceutical Company Ltd., HK inno.N Corp., KANGSTEM BIOTECH Co., Ltd., Medipost Co., Ltd., Helixmith, Reyon Pharmaceutical Co., Ltd. and GeneOne Life Science, Inc. are gearing up to begin the cell and gene therapy CDMO business, the report noted.

Brian Yang
Managing Editor

'Constantly Being Chased': Cutting-Edge Gene Therapy Developers Moving Fast In China

Plagued by a scandal which gained global attention a few years go, the gene therapy sector has recovered and is now thriving in China. But a drive for innovation, combined with ready cash for aspiring start-ups, may not translate into leaps and bounds in the field due to challenges unique to these latest treatments, including manufacturing, durability and coverage.

Eager to get ahead, gene therapy and gene-editing companies in China are now racing to secure funding and get their treatments in front of patients.

Given the promise these modalities potentially offer, it's not surprising to see such a rush into the field. But China has its own challenges in the wake of a total ban on such experimental therapies in the country just three years ago.

In November 2018, He Jiankui, a researcher at China Southern University of Technology in Shenzhen, shocked the world with an announcement of the birth of the world's first babies using gene-edited embryos. Such germline editing had long been considered a taboo no-go area for fear that such so-called "designer babies" would trigger a Pandora's box of ethics concerns.

Three baby girls were born as a result of the experiment and, amid worldwide criticism and an ethics investigation, He was eventually sentenced to three years in prison.

Yet gene-editing technology has many scientists excited about its potential, especially the use of such tools as CRISPR Cas9 to treat rare and gene mutation-related conditions such as sickle cell disease and beta thalassemia.

Three years after the scandal, China's gene-editing and gene therapy sector has rebounded and is now thriving. The speed of the recovery has been mesmerizing, even to industry insiders who observe developments daily. "I feel constantly chased," noted Li Yun, head of research and de-

velopment at EdiGene Inc, a leading gene-editing developer in the country.

Speaking at a conference on gene and cell therapy development in Shanghai on 24-25 February, Li said the general speed of progress had prompted the Beijing-based company to keep innovating around product development.

The Beijing Zhongguancun Hitech Park-based venture has teamed up with MIT and Broad Institute's Feng Zhang and Zhang's startup Arbor Biotechnologies to access Arbor's CRISPR-based cell therapy targeting cancer. A additional deal with domestic cell therapy startup Neukio Biotherapeutics, founded by veteran Richard Wang, will explore allogeneic induced pluripotent stem cell (iPS) and chimeric antigen natural killer (CAR-NK) cell therapies.

IIT: SAME BED, DIFFERENT DREAMS

Investigator-initiated studies have emerged in China as the best way to quickly provide much needed clinical data, but the practice in the country is still somewhat murky and can be a double-edged sword.

While China allows trials for experimental cell and gene therapies to be started by physicians or developers, regulatory agencies over health facilities the National Health Commission tightened its oversight after a controversial tragedy. Wei Zexi, a 21 year-old college student, died in 2016 after receiving an experimental DC-CIK treatment for his sarcoma at No.2 Armed Police Hospital, and the administration of such treatments was thereafter only allowed in qualified hospitals and physicians. (Also see "China Surprises With First CRISPR Trial Despite Regulatory Lag, Concerns" - Scrip, 25 Jul, 2016.)

Compared to novice start-ups, physicians at these nationally-recognized hospitals have easier access to patient pools and can start studies quickly. But one potential downside is also evident, in that some physicians have developed their own in-house cell therapies and so may not give equal attention to studies from these these developers.

Shanghai-based gene therapy company Belief Biomed Inc., founded by Xiao Xiao, a professor at North Carolina University in the US, become the first developer to obtain an investigational new drug approval for BBM-H901, a hemophilia B treatment in China, using a modified version of an adeno-associated virus (AAV) vector. The Shanghai firm has so far collected data from 10 patients over one to two years in an investigator-initiated study conducted at the China Hospital of Hematology under the China Academy of Medical Science. Only one participant has had any bleeding episodes.

These positive findings in turn helped Belief secure the IND and series B funding, after an initial financing round from leading venture capital partners including Qiming Capital.

But the Tianjin-based hospital was also conducting a trial with its own gene therapy for the same indication, disclosed Xue Feng, a hematologist who spoke at the Shanghai meeting. The physician-led study achieved similar, although not quite as good, results as Belief's BBM-H901, Xue noted.

READY FUNDING, REGULATORY SUPPORT

With new gene developers now popping up quickly in China, funding is following. Belief's Xiao told Scrip that the company, established only around five years ago, is now moving onto a series C financing.

The rush towards gene therapy in China is now so pronounced that even academics are leaping into the fray. Rao Yi, a renowned neuroscientist who graduated from the University of California San Francisco, founded a start-up, Grit Science, in September 2019 and has already secured CNY100m ($15.8m) in initial funding. Lead investors include the major domestic investment bank Renaissance Capital.

Meanwhile, more established gene therapy firms are speeding up their development pace to enter the clinic. Wuhan-based Neurophth Therapeutics, Inc. is leading the pack in developing a gene-based treatment for the rare eye disorder leber hereditary optic neuropathy, one among a range of ophthalmology conditions that have seen many companies flocking in following the approval of Roche Holding AG/Spark Therapeutics, Inc.'s Luxturna (voretigene neparvovec) for biallelic RPE65 mutation-associated retinal dystrophy.

Founded by Wuhan-based physician Li Bin, Neurophth secured CNY400m in a B round and soon afterwards obtained a further $60m in a series C funding, led by Sequoia Capital China.

Meanwhile, to accelerate the development of promising gene and cell therapies, Chinese regulators are moving to grant the green light to clinical studies. Swiss giant Novartis AG, for instance, has obtained approval to start a study with Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy in China. Already approved and marketed in the US and Japan, it is the first gene therapy for the devastating progressive neuromuscular condition.

Despite facing potential formidable competitors such as BioMarin Pharmaceutical Inc. and uniQure N.V., Belief's Xiao is not deterred. China has a large population with rare bleeding disorders and the cost of standard treatments such as Factor XI and the routine infusions required to prevent bleeding episodes can cause a heavy financial burden on many hemophilia B patients.

MANUFACTURING, DURABILITY ISSUES

Despite the favorable regulatory tailwinds, one potential lingering concern is the still strict controls in China over the collection, storage, import and export of genetic material samples. Extensive administrative approvals are required, which has delayed the inclusion of China in some multinationals' global clinical studies.

The sweeping Chinese biosecurity law enacted in 2021 poses generally higher hurdles for overseas gene and cell therapy developers eyeing the market. (Also see "China Tightens Clinical Study Grip In Sweeping Biosecurity Law Proposal" - Pink Sheet, 26 May, 2020.)

On top of this and unlike small molecule drugs and biologics, individualized treatments such as gene and cell therapies also have one distinctive extra layer to take into consideration - manufacturing complexity.

Li Zonghai started his pursuit of a cell therapy for solid tumors such as liver cancer in China back in 2015, the chairman and CEO of CARsgen Therapeutics, which now has two cell therapies in clinical development in the US, said during the Shanghai meeting's panel discussion, noting that China still lacks clinical data and practice in the field.

Only armed with long-term clinical data can patterns be identified, he stressed. While gene therapy is considered a one-time cure, there is still a lack of long-term efficacy, safety and durability results, the longest of which so far cover only a five-year span.

Deeming the "process is the product," many Chinese gene developers say there is still a long way to go before catching up with their US counterparts, despite China now catching up quickly in terms of number of trials.

Even so, "don't look at the figures, you have to look at the quality," advised Richard Wang, founder of Neukio Biotherapeutics and former CEO of Fosun Kite Biotechnology Co Ltd told the audience. Many Chinese developers are still concentrating on single therapeutic targets such as CD19 and there is also a lack of an industry ecosystem.

WHO FOOTS THE BILL?

Although having two marketed cell therapies, China is nowhere near offering reimbursement to pricey gene-based treatments, even if these sail through the regulatory process in the next year or so.

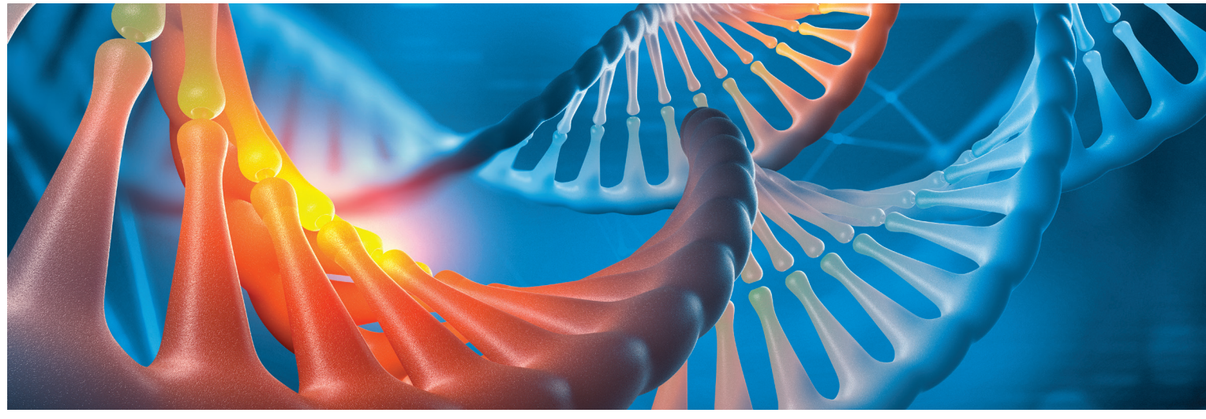
The currently approved therapies, Yescarta (axicabtagene ciloleucel) from Fosun-Kite and Carteyva (relmacabtagene autoleucel) from JW Therapeutics Co., Ltd, are priced at CNY1.2m and CNY1.29m, respectively. This is still hefty for patients in China, despite these levels being around 50% cheaper than gene therapies in the US, underscoring a large reimbursement challenge ahead.

While similarly expensive treatments such as immuno-oncology antibodies have been covered by China's vast but basic national health insurance scheme, cell and gene therapies won't fit the same bill, stressed Wang. One distinguishing aspect is one-time use, which leaves no need for re-dosing or lifetime treatment, and so "pay-for-performance" should be incorporated into any coverage of such therapies in China.

"Values dictate the prices," said another cell therapy development executive, JW Therapeutics CEO James Li.

Citing hemophilia as an example, Belief's founder and chief scientific officer Xiao said gene therapies for rares diseases should be priced on their broader value. Many hemophilia patients in China are effectively handicapped due to the lack of timely treatment, he observed.

A one-time "cure" would offer long-term protection from bleeding episodes and reduce the need for blood factor infusions, he added.



KOREA

Jung Won Shin
Senior Editor

Korean Biopharmas Rush To Boston: What Are The Challenges & Opportunities?

The head of the US arm of a major Korean government development institute talks to Scrip about why biotechs and pharma firms are flocking to Boston, how the organization is providing support and what the main challenges are.

"Boston, where an outstanding bio ecosystem is established, is the place Korean firms should go and want to go," declares Soon-Mahn Park, chief representative of the US arm of the Korea Health Industry Development Institute (KHIDI), a government institution charged with developing policies for the healthcare industry, supporting R&D and supporting businesses, and helping promote the country's interests in the sector.

From late last year, and more clearly from 2022, Park sees more Korean companies setting up companies or other operations in the US. Previously, while many wanted to enter the country, some weren't quite prepared either financially or in terms of clear strategies, the senior official said in an interview with Scrip on the sidelines of the recent Bio Korea 2022 conference and exhibition in Seoul.

But now, Korean companies have become more aggressive amid increasing globalization and the drive towards innovation to seek growth, helped by the encouragement from the KHIDI, health ministry and the pharma industry associations. The institute, for example, moved its US office from Los Angeles to Boston, a major hub for the US biotech sector, to enable direct support to companies wanting to locate there.

"Korean firms enter the US for several reasons. They may go there to conduct clinical trials with their pipeline and get FDA approvals and in the process may want to sell their R&D assets," said Park. "Many big pharmas monitor companies in Boston, invest in their pipelines and resell these at higher prices. Such a profit model has been long established; Korean firms have recently begun to join this move and among these, Yuhan Corporation has been quite active."

Yuhan, which had been largely focused on the domestic market, set up a global strategy department a few years ago to bet its future on pursuing international development, including bringing in advanced technologies and seeking clinical development and commercialization overseas. Through its US offices in San Diego and Boston, the company aims to search for promising assets, it has stated. (Also see "No More Big Fish In A Small Pond: Yuhan Opts For Globalization For Long-Term Growth" - Scrip, 21 May, 2019.)

'K-BLOCKBUSTER' PROJECT

As part of a project to support potential so-called "K-blockbuster" in the US market, KHIDI has selected 10 firms, including Voronoi, Ari Bio, Ildong Pharmaceutical Co., Ltd., Yuhan USA, Hanmi Pharmaceutical Co., Ltd. and Huons Co., Ltd., to connect with the Cambridge Innovation Center (CIC), an incubator where the KHIDI-USA office is based.

Located at Kendall Square, the core of the Boston bio ecosystem, CIC offers co-working spaces and private offices, along with a "venture café" providing networking opportunities. Tenants include start-ups, corporate innovation spin-outs and venture capital funds.

Under the initiative, the KHIDI will support office rental fees for the selected Korean firms for up to three years. The companies will also receive administrative support for setting up local operations or or offices, as well as consultative advice on out-licensing, R&D planning, regulatory approval, clinical trial, investors relations meetings and investment attraction activities. While the office rent support is limited to 10 firms, others are coming anyway, mostly to CIC or nearby areas, because of their needs, Park observed.

Currently, there are about 20 Korean biopharma firms in Boston, including Orum Therapeutics, Standigm and OliX Pharmaceuticals, Inc., and the number is expected to reach about 30 by year-end. While Yuhan has been the most active, others such as Daewoong Pharmaceutical Company Ltd., Ildong, Hanmi and Huons have already set up offices there this year or are slated to do so later this year.

For its part, the KHIDI has been jointly hosting networking events to which prominent speakers including officials from the Food and Drug Administration or National Institutes of Health have been invited and provide opportunities for education and information exchange.

> "Here [at Kendall Square] everything is located nearby so people can connect and meet easily...you can easily see Nobel Prize winners sitting at Starbucks."
>
> - KHIDI US Head Soon-Mahn Park

So what the main reasons for the Korean influx? In Park's view, "Here [at Kendall Square] everything is located nearby so people can connect and meet easily. For example, when you walk in the street, you can easily see Nobel Prize winners sitting at Starbucks."

More widely, Boston is home to over 1,000 biotech startups and global pharma firms, corporate and other research institutes, hospitals and top-rated universities. "Boston is where we can see the biggest amount of fund inflows because there are many firms, researchers, medical institutions and good technologies; it also has the highest number of biotechs that launch IPOs," he noted.

HIRING AN UNEXPECTED CHALLENGE

When smaller Korean companies first arrive in the US, they require all kinds of assistance to set up an office, while bigger firms usually ask for help for issues such as recommending principal investigators for clinical trials, contract research firms or consultants. But commonly, most types of company want to receive investments from VC partners.

"These challenges can be expected. But ironically, the single biggest challenge for them is hiring a good workforce. There are too many jobs but not enough workforce with the standards they are looking for," Park told Scrip. "The wage levels are too high while there are so many companies, so people don't tend to stay at one place for long. They easily move to other companies and because of this companies are always hiring."

For example, one Korea firm hired scientists but they left the company in just 10 months or so - this can be a particularly big blow for smaller companies, especially if they have invested in training.

The challenge was discussed at a KHIDI seminar but there don't seem to be easy answers as companies can't just offer limitless amount of money to employees. Some have suggested offering various other incentives such as more flexible working practices or stock options but this also may not be easy; this is a common dilemma for companies in Boston, Park said.

KOREA, US ECOSYSTEM DIFFERENCES

While the Boston ecosystem has been created voluntarily and not led by certain particular entities or initiatives, in South Korea, various government support programs and incubation programs have been played a more pivotal role in fostering the biotech startup sector.

"Korea has all the [necessary] factors. However, there could be a gap in standards and also a gap in time. Boston has been doing this for so long, we still can't catch up with their basic research and technology levels," the KHIDI official conceded.

Among the Korean firms in Boston, Genosco, Inc. seems to be the only one so far to achieve major success. It and parent Oscotec Inc. licensed out the lung cancer candidate lazertinib to Yuhan, which then eventually did a major $1.2bn deal with Janssen Biotech Inc. in 2018. (Also see "Yuhan Strikes Long-Awaited Lung Cancer Deal Through Huge Janssen Alliance" - Scrip, 5 Nov, 2018.)

"Genosco has become a sort of role model among Korean bioventures. They came to Boston in 2008 and successfully licensed out lazertinib to Janssen. Since then, they have moved out of the center and relocated to a new headquarters in Boston and have been expanding the R&D portfolio," Park said.

"But several other firms are certainly expected to be recognized for their technology going forward - we just need some time."

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Korea's Home-Grown New Drug Approvals Hit Record High In 2021

Jung Won Shin
Senior Editor

South Korea had a milestone year in terms of domestic new drug approvals in 2021, with multiple major pharma firms gaining nods for their in-house developed products, including the country's first COVID-19 therapeutic, from Celltrion.

South Korea's Ministry of Food and Drug Safety (MFDS) approved five home-grown new drugs in 2021, marking the highest ever number and a sharp turnaround from zero in 2020, as major domestic pharma firms' efforts to shift their focus to innovative therapeutics began to pay off. The country also gave a nod to its first domestically-developed COVID-19 treatment.

The numbers appear to reflect the more active pursuit of novel therapeutics through alliances and open innovation by major traditional companies, supported by higher R&D investment and an intention to enter global markets to seek further growth.

Several firms have also reached sizable worldwide out-licensing deals for core pipeline assets in recent years; Yuhan Corporation's Leclaza (lazertinib) and Hanmi Pharmaceutical Co., Ltd.'s Rolontis (eflapegrastim), for instance, are undergoing late-phase international clinical trials through their respective partners, Janssen Pharmaceutical Cos. and Spectrum Pharmaceuticals Inc.

In addition, other large domestic firms such as global biosimilars specialist Celltrion, Inc. have been actively diversifying into new drug development.

Among those receiving marketing authorizations over the course of last year, Yuhan's Leclaza was approved in January for second-line use in advanced non-small cell lung cancer. The regulatory OK was based on Phase II data but granted on condition the company conduct a Phase III trial after the approval. Leclaza is indicated specifically for the treatment of patients with EGFR T790M mutation-positive, locally advanced or metastatic disease previously treated with an EGFR tyrosine kinase inhibitor. (Also see "World-First Nod For Yuhan's Lung Cancer Drug, In Korea" - Scrip, 19 Jan, 2021.)

Celltrion's anti-COVID-19 monoclonal antibody Regkirona (regdanvimab) was approved in February, becoming the first domestically developed therapeutic for the pandemic to be cleared in the country and following positive top-line results in a global Phase II trial.

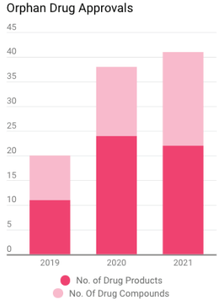
It was the second drug to receive official approval in the country for the treatment of COVID-19 following Gilead Sciences, Inc.'s antiviral remdesivir, and is recommended for use in high-risk adult patients with mild-to-moderate symptoms. The nod was granted on the condition that Celltrion conduct a Phase III trial. (Also see "Celltrion Antibody Becomes First Home-Grown COVID-19 Drug Approval In Korea" - Scrip, 8 Feb, 2021.)

Home-Grown New Drug Approvals

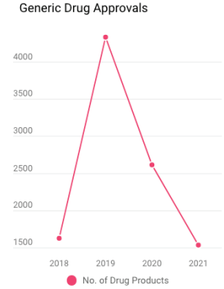
In 2021, 37 new drug products (28 drug compounds) and 22 orphan drug products (19 drug compounds) were approved by the MFDS, while a total of 2,270 drug products were approved or notified.

(source: MFDS)

Orphan Drug Approvals



Generic Drug Approvals



Hanmi's Rolontis, a long-acting granulocyte colony-stimulating factor, gained an approval in March and is used for neutropenia in patients receiving myelosuppressive anticancer drugs. (Also see "World-First Korean Nod For Hanmi's Neutropenia Contender Rolontis" - Scrip, 23 Mar, 2021.)

Daewoong Pharmaceutical Company Ltd.'s Fexuclue (fexuprazan), a next-generation molecule for erosive esophagitis, followed in December, becoming the second original potassium-competitive acid blocker to be approved in the country after CJ Healthcare's K-Cab (tegoprazan) in 2018. (Also see "Daewoong's P-CAB Contender Holds Up Well At Phase III" - Scrip, 11 May, 2020.)

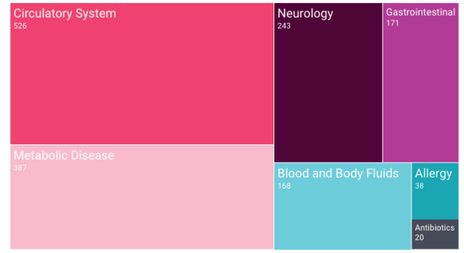
GENERIC APPROVALS FALL SHARPLY

In 2021, the MFDS approved a total of 37 new drug products, comprising 28 new compounds, while 22 orphan drug products (19 new compounds) were approved, remaining steady versus a year earlier.

As South Korea joined in the worldwide efforts to speed up the development and administration of COVID-19 vaccines, the country granted clearances to several vaccines developed by global companies including AstraZeneca PLC, Pfizer Inc., Janssen and Moderna, Inc. last year, while no domestically developed shots against SARS-CoV-2 have been approved so far.

Meanwhile, approvals of generics fell a precipitous 41% from 2020, affected by a revision to the Pharmaceutical Affairs Act that limited the number of generics that can share identical bioequivalence test data to three products.

Approvals By Therapeutic Sector (No. of drug product)



With the implementation of a new law on support for cutting-edge biologics (advanced regenerative medicine and advanced biopharmaceuticals), three gene therapies from Novartis AG were approved, while 15 already approved cell therapies were granted re-approvals again under the new law. (Also see "Cutting-Edge Biologics Approvals, Trials Pick Up In Korea After New Law" - Pink Sheet, 9 Dec, 2021.)

List Of Korea's New Drug Approvals In 2021 (in terms of drug compounds)

Drug	Company	Approval Date	Category
Galafold cap.	Handok	Jan28	gastrointestinal
Bavencio inj.	Merck	Aug 05	anti-cancer
Byfavo inj.	Hana Pharm	Jan 07	general anesthetics
Leclaza tab.	Yuhan	Jan 18	anti-cancer
Vyzulta eye drops	Bausch Health Korea	Feb 05	ophthalmic
Regkirona inj.	Celltrion	Feb 05	respiratory
Calquence cap.	AstraZeneca	Feb 05	anti-cancer
AstraZeneca COVID-19 Vaccine	AstraZeneca	Feb 10	vaccine
Takhzyro inj.	Takeda	Feb 26	circulatory system
Comirnaty	Pfizer	Mar 05	vaccine
Kymriah inj.	Novartis	Mar 05	anti-cancer
Rolontis prefilled syringe inj.	Hanmi Pharm	Mar 18	blood/body fluids
COVID-19 Vaccine Janssen	Janssen	April 07	vaccine
Bronpass tab.	Hanlim Pharm	April 09	respiratory
Aklief Cream	Galderma Korea	April 27	skin emollient
Piqray tab	Novartis	May 13	anti-cancer
Moderna Spikevax	GC Pharma	May 21	vaccine
Zolgensma inj.	Novartis	May 28	CNS
Evrenzo tab.	AstraZeneca	July 09	blood/body fluids
Fremanezumab inj.	Handok Teva	July 27	CNS
Shingrix inj.	GSK	Sept 06	vaccine
FACBC inj.	Duchem Bio	Sept 17	radiopharmaceutical
Nerlynx tab.	Bixink Therapeutics	Oct 19	anti-cancer
Cibinqo tab.	Pfizer	Nov 23	autoimmune
Verquvo tab.	Bayer	Nov 30	circulatory system
Dysval cap.	Mitsubishi Tanabe	Nov 30	CNS
Ozanex Cream	Bukwang Pharm	Dec 10	purulent disease
Fexuclue tab.	Daewoong Pharm	Dec 30	peptic ulcer

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