

SCRIP ASIA 100

CITELINE COMMERCIAL



2024

ICON

Foreword

The Asia-Pacific region, like the rest of the world, continues to move back to some form of post-pandemic normality – although not everything is going as expected.

China was widely forecast to experience a rapid economic rebound following the lifting of its tough COVID restrictions in late 2022, but in reality is recovering more slowly than predicted. The larger challenges making the headlines include weak consumer confidence and spending, high unemployment among younger workers, a simmering property crisis and share sell-offs by foreign investors.

Although the longer-term impact of these factors on the pharma sector is not yet clear, a renewed anti-corruption drive in the health arena has seen many companies rapidly reduce sales and promotion activities. While many foreign pharma firms continue to be concerned about the state of US-China relations, a positive sign is that top-level visits by officials are resuming is a possible signal that geopolitical tensions may be topping out.

Japan, as the largest mature biopharma market in the region, continues along in a less dynamic but predictable fashion, research-based industry concerns there continuing to center on the fine-tuning of the reimbursement pricing system and on continued regular one-off price cuts for fast-selling products. Supply shortages initially stemming from quality concerns continue to plague the generics sector.

While Japan's top firms already have a well-developed international presence, the focus of South Korea's industry now seems very much to be on building up a similar global footprint, helped by multiple government-supported programs and steadily rising R&D capabilities for novel drugs. This push for innovation is also reflected in China, which continues to make rapid surges in areas such as antibody-drug conjugates and immune-oncology, with western firms entering multiple licensing deals to access valuable new assets. India continues to be a global generics powerhouse, but some of the largest companies there remain concerned about pricing pressures in the US. Alongside, there have been investments in new technologies, markets and specialty products, with in some cases a steady build-up in original R&D. More recently, there have been signs that some prominent founding families are considering stepping back as their companies eye the next stage in development.

More broadly, moves to repatriate supply chain links are continuing as a legacy of the pandemic, as does the adoption of remote and digital tools that was accelerated during the toughest challenges of COVID-19. While we've seen no landmark mega M&A deals since last year's edition, there have been some substantial asset-specific alliances. Takeda's late 2022 agreement with Nimbus Therapeutics for the Phase II TYK2 inhibitor TAK-279 was the prime example of this, being worth a whopping \$4 billion upfront.

This introduction necessarily picks out only some of the key top-line trends and, as always, we hope the carefully curated selection of data, insights and analysis in this year's *Scrip Asia 100*, including extensive content from our on-the-ground team, will help you dig deeper into these and other issues to help make sense of this large, diverse and complex part of the pharma world.

Ian Haydock

Editor-in-Chief, APAC
Citeline

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Regulatory Reforms Enhance China's Biotech Trial Potential



Lina Feng, Director,
Global Regulatory Affairs, ICON China

China has rapidly established itself as an attractive option for clinical trials, with activity trending upwards year on year over the last decade. In fact, for the first time in 2021 China overtook the US as the top destination for trials, with 3,795 new clinical trials initiated there compared to 3,310 in the US.¹

There has long been great potential for international biotech companies that pursue studies in China, with its large population facilitating reduced patient recruitment timelines and lower study start-up (SSU) costs. However, the complex regulatory environment may have dissuaded some sponsors from considering China as a study location for multi-regional clinical trials (MRCTs). Now, following significant reforms and the Chinese National Medical Products Administration (NMPA) becoming a regulatory member of the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use, there is a renewed opportunity for biotechs to reap the benefits of trials in China.

OPTIMIZED CLINICAL TRIAL APPLICATION & REGISTRATION PATHWAYS

Once a clinical trial application (CTA) has been accepted for review, timelines for approval have been standardized to 60 working days under the new regulatory framework. This is a notable improvement on the two- to three-year period it could previously take. Moreover, sponsors are permitted to initiate studies if no objection is received from China's Center for Drug Evaluation (CDE) in that timeframe, placing the burden on review bodies under a tacit approval model.

The CDE also offers multiple channels to support sponsors with studies and marketing authorization application (MAA) submissions, including communication meetings to clarify any uncertainties. These meetings are free of charge, which is particularly helpful for biotechs looking to manage their financial resources carefully.

Additionally, restrictions on registering imported medicinal products for use in clinical trials have been reduced, enabling sponsors to conduct research in China much earlier. Previously, in order to be used in a study in China, the product needed to have already commenced Phase II or III trials in other countries. However, under revised guidance, sponsors can now start Phase I studies in China in parallel with those



Qing Liu, Senior Director,
Project Management, ICON China

in other locations. As a result, biotech companies can capitalize on the advantages China can offer their studies in early development and expedite progress.

There are also further benefits for overseas sponsors wishing to access the Chinese market after their products progress through clinical studies. The prior requirement stipulating an imported product must be authorized in its country of origin before MAA submission in China has now been removed. NMPA has also introduced measures to encourage the development of innovative products and those for unmet clinical needs (e.g. rare disease and pediatric indications) such as breakthrough procedures, conditional approval and priority review processes. As China is the second largest health care market, this is valuable for companies looking for commercial success and it also increases prospects for Chinese patients looking for improved treatment options.

SOLUTIONS EXIST FOR REMAINING CHALLENGES

While the reforms made to clinical trial processes in China are very encouraging for biotech sponsors, there are underlying distinctions to studies carried out here that may dissuade companies from considering the location. Nevertheless, there are ways to overcome these obstacles.

Local treatment practices and guidance

There are local nuances to treatment practices and guidance in China that international sponsors may not have an in-depth understanding of, especially if conducting trials in the region for the first time. For this reason, it is very important to involve key opinion leaders (KOLs) as early as possible. These experts can provide suggestions on protocol design, support communication with the CDE, recommend principal investigators (PIs), help with site identification, and accelerate SSU timelines.

When identifying sites, biotechs must note that in China most are independent and, consequently, their requirements differ. Even the same site may change their conditions from one year to the next, so it is critical that sponsors check before any submission. Again, KOLs and local expertise are very helpful when navigating these complexities.



During the trial, it is also best to assign a medical monitor based in China, as they can uphold trial efficiency by removing language and time-zone barriers to quickly address any questions that may arise from the PI. If sponsors have local presence this could be a member of their own team, but as many US- or Europe-headquartered biotechs do not have such workforces, contract research organizations (CROs) can assist.

Competing trials

While the exponential growth of trials in China has greatly increased site and PI experience, as this continues some sponsors may find themselves competing to secure availability. One strategy is to target more sites in what may be referred to as “Tier 2/3” cities instead of highly oversubscribed “Tier 1” cities. While these sites may not have as much direct experience, training can be provided to ensure studies still run effectively and they will likely have untapped patient pools which can accelerate enrolment.

There are also recruitment and retention services available for sponsors should they struggle with enrolment. Partners have their own databases and networks of community hospitals and clinics which biotechs would otherwise not be able to access. Many CROs now have this capability in-house, but they can also form local partnerships with specialist providers to build targeted strategies for recruitment, depending on the therapy and patients required.

Communication and time zone differences

One of the key concerns from US- and Europe-based biotech companies when considering trials in China is the lack of control and communication they may have, due to significant time zone differences and language barriers. As a result, it is recommended that all trials have a China-based clinical trial manager (CTM) who is familiar with local practices, culture, and dialect, whilst also having a project manager (PM) in the sponsor’s own time zone.

PMs can facilitate ongoing cross-functional conversations easily with the local CTM to ensure there is no breakdown in communication, while ensuring dedicated resource in the location of the trial to maintain progress. As part of this, there should also be clear escalation pathways in the event that challenges arise and other stakeholders need to be pulled in.

BENEFITS AWAIT FOR BIOTECHS

While there are no doubt challenges to conducting trials in China for biotechs based in the US and Europe, for those that persevere there are clear benefits to be realized. China is the most populous country in the world, but it has relatively untreated patients in a number of key therapeutic areas such as immuno-oncology and chronic diseases.² This leads to recruitment timelines that are estimated to be around two to three times faster, which is critical for biotech companies racing to generate positive clinical data and secure further investment.

Costs are also lower than in the highly competitive US and European markets for trial start-up and enrolment. Generally, even at top urban medical centers, direct costs are around 30% lower than in the US.² For early-stage sponsors progressing one of their first assets to the clinic, every bit of financing needs to stretch as far as it can, so savings such as this could be pivotal to move through development.

Most of the barriers to achieving these advantages can be overcome with understanding of the Chinese trial environment and requirements. For biotechs without a local presence in China, it is highly unlikely they will already have this in-house, so partnerships with specialists are the way forward.

Established CROs can utilize their experience and expertise to guide international sponsors through the nuances of China’s regulatory and clinical processes, to avoid any delays or errors that require rectifying at a later stage. As China continues to gain momentum as a key study location and requirements continue to evolve, this will be key to ensuring trial success.

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SCRIP ASIA 100: 2022 PHARMACEUTICAL SALES

RANK	COMPANY	LATEST PHARMA SALES (\$M)	PHARMA SALES % CHANGE	RANK	COMPANY	LATEST PHARMA SALES (\$M)	PHARMA SALES % CHANGE
1	Takeda	30842	-5%	26	Harbin Pharmaceutical Group Co., Ltd.	2055	4%
2	Astellas	11629	2%	27	Kyowa Hakko Kirin	1944	-39%
3	Daiichi Sankyo	9235	107%	28	Livzon Pharmaceutical Group	1880	1%
4	Otsuka Pharmaceutical	8714	-2%	29	Shijiazhuang Yiling Pharmaceutical Co.,Ltd	1865	19%
5	Eisai	5701	-17%	30	Celltrion	1774	6%
6	Sun Pharmaceutical	5512	6%	31	Glenmark Pharmaceuticals	1654	-1%
7	Shanghai Fosun Pharmaceutical Group	4569	2%	32	Topcon Corp.	1651	309%
8	Sino Biopharmaceutical	4284	3%	33	Towa	1599	13%
9	Sumitomo Dainippon Pharma	4254	-9%	34	Sawai	1534	-13%
10	Mitsubishi Tanabe Pharma	4100	17%	35	Meiji Holdings	1511	-12%
11	Shanghai Pharmaceutical Group Co., Ltd.	3983	2%	36	Sinovac Biotech Ltd.	1493	-92%
12	CSPC Pharmaceutical Group Ltd.	3908	20%	37	Biocon	1410	27%
13	Asahi Kasei Pharma	3805	0%	38	CR Double-Crane Pharmaceuticals Co., Ltd	1406	0%
14	Jiangsu Hengrui Medicine Co. Ltd.	3139	-22%	39	Jiangsu Hansoh Pharmaceutical	1397	-9%
15	Dr Reddy's	3131	22%	40	Yuhan Corp	1379	-6%
16	Aurobindo	2983	-6%	41	GC Biopharma (Green Cross)	1329	-1%
17	Cipla	2898	-1%	42	Beigene	1255	98%
18	Sichuan Kelun Pharmaceutical	2815	5%	43	Shenzhen Hepalink Pharmaceutical Group Co., Ltd.	1235	25%
19	Joincare Pharmaceutical Group Industry Co., Ltd.	2552	3%	44	KPC Pharmaceutical Inc.	1233	-4%
20	Samsung Biologics	2331	70%	45	Zhejiang Huahai Pharmaceutical Co., Ltd.	1219	18%
21	Ono	2259	1%	46	Torrent Pharmaceuticals	1215	7%
22	Shandong Buchang Pharmaceuticals Co., Ltd.	2226	-9%	47	3SBio	1187	22%
23	Zydus Lifesciences (earlier Cadila Healthcare)	2219	9%	48	Teijin Pharma	1167	-30%
24	Santen	2074	-9%	49	Chong Kun Dang	1156	-2%
25	Lupin	2072	-5%	50	Kwang-Dong Pharmaceutical	1112	-5%

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51	Luye Pharma Group Ltd.	1035	7%	76	Takara Bio Inc.	598	-3%
52	Hanmi Pharm	1034	-2%	77	Zhuzhou Qianjin Pharmaceutical Co., Ltd.	594	5%
53	Daewoong Pharmaceutical	994	-1%	78	Boryung	591	106%
54	Hisamitsu	983	-10%	79	Jeil Pharmaceutical	561	-15%
55	Shanghai RAAS Blood Products Co., Ltd.	973	46%	80	Kaken	559	-19%
56	Nippon Shinyaku	934	-15%	81	Yichang HEC Changjiang Pharmaceutical Co.	557	293%
57	Zhejiang Conba Pharmaceutical Co., Ltd.	882	-8%	82	JW Pharmaceutical Corporation	532	0%
58	Kyorin	867	-10%	83	Zeria Pharmaceuticals	524	9%
59	Shandong Lukang Pharmaceutical Co., Ltd.	829	9%	84	Dongkook Pharm	514	-1%
60	SSY Group Limited	822	19%	85	Kissei	501	1%
61	Jubilant Pharmova (earlier Jubilant Life Sciences)	798	-4%	86	Il-Dong Pharm	495	1%
62	Mochida	791	-16%	87	Dong-A ST	494	-5%
63	Laurus Labs Ltd.	769	15%	88	Strides Pharma	470	13%
64	Walvax Biotechnology Co., Ltd.	752	40%	89	Zhejiang JingXin Pharmaceutical Co., Ltd.	468	9%
65	Alembic	710	-1%	90	Harbin Gloria Pharmaceuticals Co., Ltd.	463	-5%
66	Shionogi	675	-73%	91	Mega Lifesciences Public Co. Ltd.	448	1%
67	CK Life Sciences	674	-3%	92	Hutchison China MediTech	426	20%
68	Hualan Biological Engineering, Inc.	666	-3%	93	Toray Industries	398	-18%
69	Maruho	660	-17%	94	Japan Lifeline Co., Ltd.	396	-15%
70	HK inno. N (formerly CJ Healthcare)	658	0%	95	Nippon Kayaku	396	-17%
71	PT Kimia Farma	648	-28%	96	Huons Co., Ltd.	382	0%
72	Jiangsu NHWA Pharmaceutical Co., Ltd.	640	5%	97	Torii	374	-13%
73	Jiangsu Kanion Pharmaceutical Co Ltd	637	13%	98	Guangxi Wuzhou Pharmaceutical Group Co. Ltd.	365	-26%
74	Japan Tobacco	635	-13%	99	SK Bioscience	355	-1%
75	Innovent Bio	616	-1%	100	Betta Pharmaceuticals Co., Ltd.	354	2%

Editor's Note: This table was updated on 31 January 2024 to correct sales figures for Daiichi Sankyo.

CHINA TOP 20 PHARMACEUTICAL COMPANIES BY SALES

RANK	COMPANY	2022 PHARMA SALES (\$M)	CHANGE FROM 2021 (% BASIS)
1	Shanghai Fosun Pharmaceutical Group	4569	2%
2	Sino Biopharmaceutical	4284	3%
3	Shanghai Pharmaceutical Group Co., Ltd.	3983	2%
4	CSPC Pharmaceutical Group Ltd.	3908	20%
5	Jiangsu Hengrui Medicine Co. Ltd.	3139	-22%
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9	Harbin Pharmaceutical Group Co., Ltd.	2055	4%
10	Livzon Pharmaceutical Group	1880	1%
11	Shijiazhuang Yiling Pharmaceutical Co.,Ltd	1865	19%
12	Sinovac Biotech Ltd.	1493	-92%
13	CR Double-Crane Pharmaceuticals Co., Ltd	1406	0%
14	Jiangsu Hansoh Pharmaceutical	1397	-9%
15	Beigene	1255	98%
16	Shenzhen Hepalink Pharmaceutical Group Co., Ltd.	1235	25%
17	KPC Pharmaceutical Inc.	1233	-4%
18	Zhejiang Huahai Pharmaceutical Co., Ltd.	1219	18%
19	3SBio	1187	22%
20	Luye Pharma Group Ltd.	1035	7%

JAPAN TOP 20 PHARMACEUTICAL COMPANIES BY SALES

RANK	COMPANY	2022 PHARMA SALES (\$M)	CHANGE FROM 2021 (% BASIS)
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2	Astellas	11629	2%
3	Daiichi Sankyo	9235	107%
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11	Kyowa Hakko Kirin	1944	-39%
12	Topcon Corp.	1651	309%
13	Towa	1599	13%
14	Sawai	1534	-13%
15	Meiji Holdings	1511	-12%
16	Teijin Pharma	1167	-30%
17	Hisamitsu	983	-10%
18	Nippon Shinyaku	934	-15%
19	Kyorin	867	-10%
20	Mochida	791	-16%

Editor's Note: This table was updated on 31 January 2024 to correct sales figures for Daiichi Sankyo.

INDIA TOP 10 PHARMACEUTICAL COMPANIES BY SALES

RANK	COMPANY	2022 PHARMA SALES (\$M)	CHANGE FROM 2021 (% BASIS)
1	Sun Pharmaceutical	5512	6%
2	Dr Reddy's	3131	22%
3	Aurobindo	2983	-6%
4	Cipla	2898	-1%
5	Zydus Lifesciences (earlier Cadila Healthcare)	2219	9%
6	Lupin	2072	-5%
7	Glenmark Pharmaceuticals	1654	-1%
8	Biocon	1410	27%
9	Torrent Pharmaceuticals	1215	7%
10	Jubilant Pharmova (earlier Jubilant Life Sciences)	798	-4%

SOUTH KOREA TOP 10 PHARMACEUTICAL COMPANIES BY SALES

RANK	COMPANY	2022 PHARMA SALES (\$M)	CHANGE FROM 2021 (% BASIS)
1	Samsung BioLogics	2331	70%
2	Celltrion	1774	6%
3	Yuhan Corp	1379	-6%
4	GC Biopharma (Green Cross)	1329	-1%
5	Chong Kun Dang	1156	-2%
6	Kwang-Dong Pharmaceutical	1112	-5%
7	Hanmi Pharm	1034	-2%
8	Daewoong Pharmaceutical	994	-1%
9	HK inno. N (formerly CJ Healthcare)	658	0
10	Boryung	591	106%

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Our focus is on delivering Healthcare Intelligence to customers to address the full spectrum of clinical development challenges, not just point of service delivery. The synthesis of our experience, expertise, best practices, technology and data provides patient-centric processes, commercially optimised for global success, and is driving transformation of trials to improve R&D ROI. ICON has established relationships with a majority of the world's top pharmaceutical and biotech companies, offering:

Globally scaled expertise and 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

Clinical focus: no ownership from parent organisation and no distractions from 'near adjacencies' means we are completely committed to customers' clinical development programs.

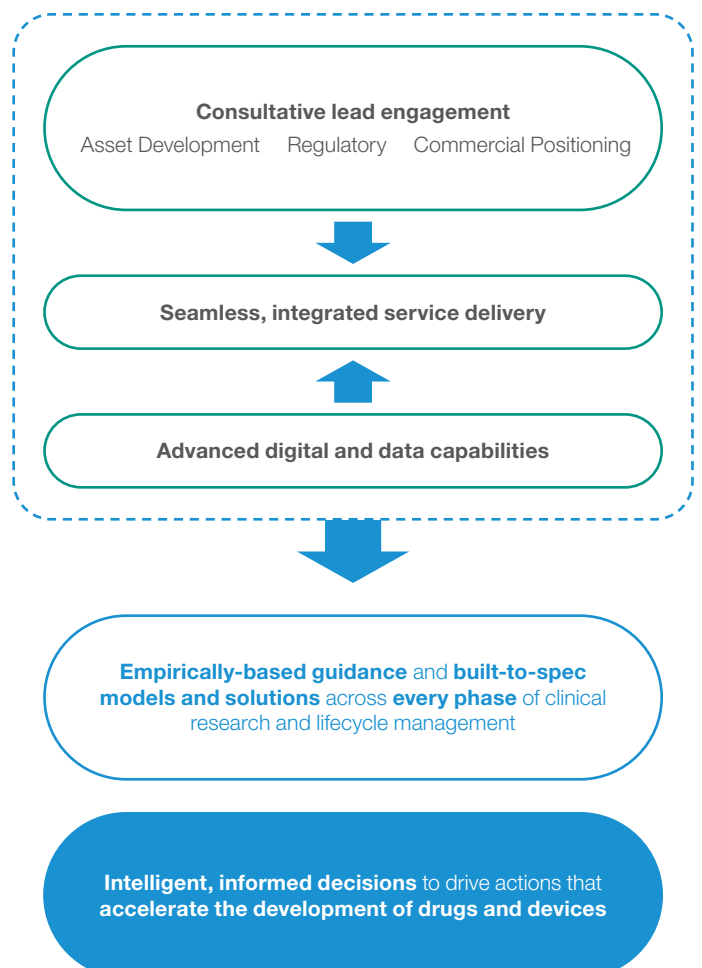
Flexible partnership models and governance structures ensure transparent communications. Regardless of the size of your organisation or your project, we work your way.

Strategy-driven delivery: At ICON, we know that clinical research now requires a more comprehensive, strategy-driven delivery. Our approach is to proactively guide clients towards the most effective, efficient solution across all modalities of research.

We commence client engagements with a strategic consultation, delivered by our team of over 700 consultants, to identify custom solutions, eliminate process white space and identify efficiencies and savings. This delivers across three areas:

- Robust asset development consulting for a deeper understanding of development pathways, asset acquisition/transfer options and access to scientific expertise across disciplines for ad hoc support.
- A network of international experts delivering superior regulatory and quality assurance strategies, submissions, and support to expedite drug and medical device development and manage ongoing global compliance.
- Integrated solutions to demonstrate the value of products and support global brand success from dedicated real-world evidence, pricing, market access, reimbursement, health economics, and medical communications experts.

This consultative-led approach, the breadth of our capabilities and advanced digital and data capabilities enables us to deliver seamless, integrated services.





Decentralised clinical trial solutions: Clinical research should engage with patients wherever they are. ICON has all the service components to deliver DCTs and the experience and expertise to provide integrated, customised solutions. Our customised, integrated decentralised clinical trial solutions can help you achieve better outcomes, while maximising recruitment and retention of diverse patient populations.

Site & patient access: Our site networks, patient recruitment expertise, in-home services and site resourcing services unlock access to millions of 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. 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 five Phase I clinical research units across the United States and Europe.

Speed to market: An extensive services portfolio, digital and technology capabilities, combined with flexible delivery and models allow us to reduce development time and costs.

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 satisfy 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.

Advanced digital and data capabilities: Innovation at ICON is focused on the factors that are critical to our clients. Investing heavily in AI, machine learning and RPA capabilities, our portfolio of digital solutions and platforms are specifically developed for the needs for clinical research. Our enterprise clinical informatics framework ingests, integrates and interrogates the full spectrum of data sources and assets for rich, real-time data-visualisation and actionable insights to significantly enhance the efficiency and productivity of clients' development programs.

Data insights can include experiential data paired with external data, benchmark data on different models of research, predictive algorithms & continuous performance evaluation, whilst tokenisation of data extends reusability.

ICON is driving transformation of trials to improve R&D ROI and support a future landscape of many more trials delivered in shorter timeframes, but conversely of greater operational and scientific complexity. We strategically and proactively solve today's challenges without losing sight of their impact tomorrow.





Jung Won Shin
Senior Editor

Korea's Clinical Trial Landscape In 2022: Approvals Fall To Pre-COVID Levels

MSD, Janssen, Chong Kun Dang, Daewoong Top Sponsors

The *Pink Sheet* takes an infographic look at South Korea's clinical trial trends in 2022 to illustrate how the country's biopharma R&D is developing and how activities are recovering in the post-pandemic situation. One key takeaway is that approvals for trial starts have fallen back to pre-COVID levels, suggesting a falling off of activity related to drugs and vaccines for the virus.

The number of clinical trial approvals across all development phases in South Korea in 2022 sank to the level of before the COVID-19 pandemic in 2019 - but despite the drop, the country's global ranking in terms of number of such permissions improved a notch, marking its best-ever placing.

According to the Ministry of Food and Drug Safety's data for clinical trial approvals during the calendar year, the country ranked fifth globally in terms of sponsor-led study registrations, up from sixth the previous year. Korea placed third globally based on the number of single-country clinical studies, unchanged from the previous year, and Seoul continued to be the most common location for domestic trials.

While the share of European countries in multinational trials increased, Korea's ranking fell a place to 11th, although it still ranked top among Asian countries.

In 2022, although the total number of clinical trial approvals in Korea fell 15.6% to 711, the proportion of pharma company-led trials actually increased. Globally, company-led trials declined 27.7% last year, largely because of depressed investment for new drug R&D amid the worldwide economic recession and a drop in clinical trials for COVID-19 drugs, the drug ministry said. By therapeutic area, oncology led, with 259 trial approvals in Korea.

According to data from Citeline's Trialrove, antibody-drug conjugate-related clinical studies appear to be actively progressing in the country, with 172 trials for 124 drugs underway, of which 61 were at the Phase III stage.

CLINICAL SECTOR SEEN AS KEY

The clinical trial industry is seen as a key sector in Korea, where authorities are aiming to further grow it with the goal of raising the country's global trial ranking to third by 2027, as stated in an official five-year plan to foster and support the biopharma industry.

To achieve this target, the government will seek to expand participation in trials by both primary and secondary medical institutions to ease difficulties in recruiting subjects, particularly for pediatric and chronic disease studies.

The intention is to roll out a national clinical trial management system to 60 medical institutions by 2027, while strengthening incentives for the firms engaged in innovative drug R&D by benchmarking against other countries, including the US and Australia. Guidelines and improvements in regulations governing decentralized trials will be drawn up to reinvigorate patient-centric, decentralized studies using digital technology, the government has stated.

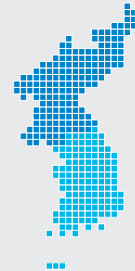
Among pharma firms, MSD, Janssen Pharmaceutical Cos., Chong Kun Dang Pharmaceutical Corp. and Daewoong Pharmaceutical Company Ltd. most actively pursued clinical trials in Korea in 2022, the data show.



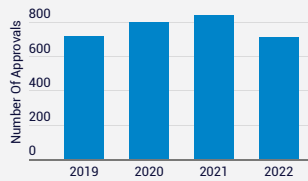
Korea's Clinical Trial Landscape In 2022

Korea ranked as the fifth major global clinical trial country in 2022 based on number of sponsor-led trial registrations versus sixth place in 2021. By city, Seoul continued to be ranked in first place, while Korea ranked third based on single-country clinical trials, unchanged from the year before.

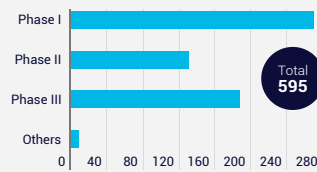
Main Features Of Korean Clinical Trials In 2022: The number of clinical trial approvals returned to pre-COVID-19 pandemic levels, the proportion of pharma-led clinical trials increased, while clinical trials for the drugs developed by Korean pharmas remained similar to 2021 levels.



Clinical Trial Approvals In Korea (2022)



Clinical Trial Approvals By Development Stage (2022)



Global Pharma-Led Clinical Trial Ranking In 2022

By Country	Rank	By City
US	1	Seoul
China	2	Beijing
Spain	3	Madrid
Germany	4	Miami
Korea	5	Houston

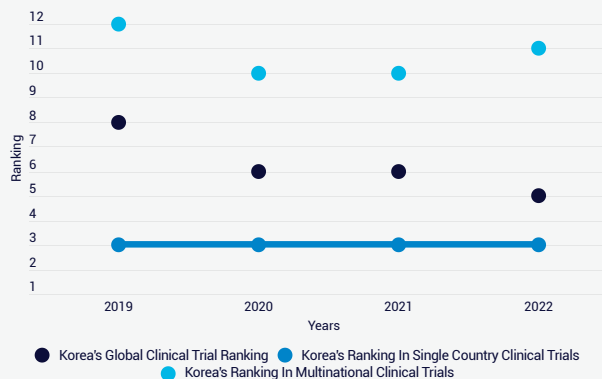
Source: MFDS

Strategic Support To Push Up Korea's Global Clinical Trial Ranking



Under the 5-year plan to foster and support the biopharma industry, the government aims to raise the country's global clinical trial ranking to third place by 2027.

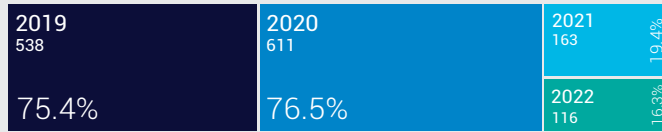
Korea's Clinical Trial Ranking



Source: MFDS

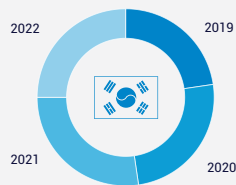
Among total clinical trial approvals in Korea in 2022, approvals given to pharma firm-led clinical trials reached 595, accounting for 83.7%, up 3.1 percentage points from 80.6%. Investigator-initiated clinical trials fell in terms of approval number and proportion.

Number (Proportion) Of Pharma Firm-Led Clinical Trial Approvals

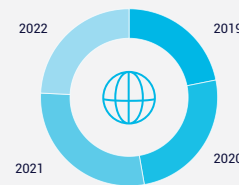


Clinical trials using foreign pharma developed drugs fell 15.1% from the year before, while trials using Korean pharma developed drugs fell 8.5%.

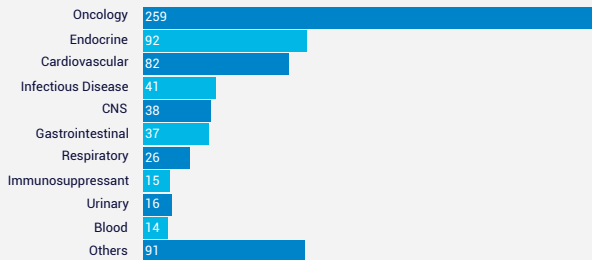
Clinical Trial Approvals For Korean Pharma Developed Drugs



Clinical Trial Approvals For Foreign Pharma Developed Drugs



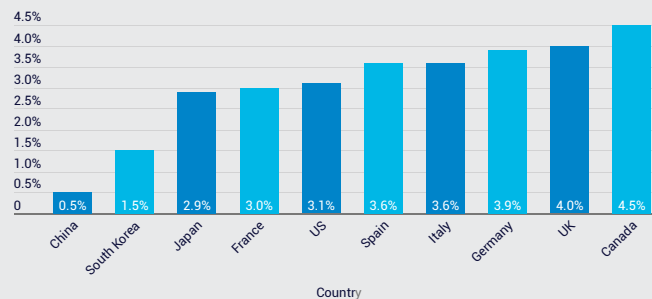
Clinical Trial Approvals By Therapeutic Area (2022)



Source: MFDS

According to Citeline Clinical's recent White Paper titled "Unlocking Potential Decentralized Clinical Trials," Asian countries, including China, South Korea, and even Japan, are lagging behind and have been more resistant to pivot towards novel trial designs. Panelists at the Clinical Trials Europe conference discussed how regulatory authorities in these markets are less open to new approaches and this creates a lack of harmonization which is a challenge for sponsors planning global clinical trials.

Percentage Of Ongoing Or Planned Industry-Sponsored Clinical Trials Incorporating DCT Attributes By Country



% of trials incorporating DCT attributes

Source: Trialtrove, February 2023



Dexter Yan
Senior Reporter

New China Trial Design Rules Stress Patient Needs And Experience

China's Center for Drug Evaluation has finalized new guidelines that stipulate sponsors of randomized controlled clinical studies should more closely consider patient needs and experience when designing trials, including a consideration of likely future changes in standard therapies.

China's Center for Drug Evaluation (CDE), the top drug review agency under the National Medical Products Administration, is newly requiring sponsors to consider the needs and experience of patients in the design of clinical trials.

The new guidance brings to the fore that clinical study sponsors should consider patients' needs and improve patient experience in trial designs. They should also in a timely and full way communicate with drug reviewers on whether patients' experience and opinions have been sufficiently expressed and adopted.

The CDE published on 27 July a pilot program for *Technical Guidelines on Patient-Centric Design for the Clinical Trials of Drugs* with immediate effect, after concluding a roughly one-year period of soliciting

industry opinions on the draft version.

Notably, although the final guidance has been kept largely unchanged from the draft, a key part of the closing remarks in the draft version has been removed.

In the draft, published in August 2022, the now removed section stated: "At the current stage, there are probably a certain degree of difficulties and challenges to carry out patient-centric clinical trial designs," raising questions over whether patients' opinions could be fully expressed, accepted and implemented.

The environment and measures to overcome such issues have yet to be completely established, the CDE noted in removing the wording, adding that practices already in place in foreign countries should be gradually promoted in China, given the domestic cultural background and considering patients' openness to such measures.

"Patient-centric clinical trial designs should be realized to suit the situation in China," the CDE stressed.

“

Since the recognized standard therapy plans are constantly amended, the selection of control groups, with appropriate expectations, will change with the passage of time.”

- China's Center for Drug Evaluation

MULTIPLE CONSIDERATIONS

The new guidelines' grip over study design appears most likely to affect the conduct of randomized controlled trials in China.

The CDE suggests that sponsors should evaluate potential dynamic changes in treatment needs in the future and choose control groups in a prospective manner, with extra attention paid to available therapies other than the best available treatments in clinical practice, after considering patients' experience in trials.

“Since the recognized standard therapy plans are constantly amended, the selection of control

groups, with appropriate expectations, will change with the passage of time,” the center explained.

Regarding patients' right to decide to pull out of a trial, the new guidelines stipulate that this should be guaranteed. Subjects should be fully informed of other available treatments, the CDE said, adding that participants should be informed in a timely manner during studies of any changes to the standard therapies for the relevant indications.

The requirements regarding control groups as set out in the new guidelines apparently evolved from prior CDE guidance.

In the *Technical Guidelines on Benefit-Risk Assessment of Novel Drugs* published in June, the CDE held that in studies with positive controls, sponsors should ensure no unacceptable benefit-risk impact or improved efficacy with a less favourable benefit-risk profile from investigational therapies when compared with existing approved therapies. The less stringent requirements were first put forward in the *Technical Guidelines on the Clinical Value-oriented Clinical Development of Anti-Tumor Drugs*, published in November 2021.

The new guidelines on patient-centricity have introduced higher-level requirements on investigational drugs in terms of efficacy and safety, analysts from China's Essence Securities commented in a research note, adding the fresh demands from the CDE are expected to promote innovation in the domestic pharmaceutical industry in the long term.

The moves towards greater patient-focused drug development in China reflect those in some other major markets. In the US, such considerations were built into the reauthorization of the Prescription Drug User Fee Act in 2012, when Congress directed the Food and Drug Administration to meet at least monthly with patients and consumers and other stakeholders while it was conducting user fee discussions with industry. (Also see “Standardization Of Patient-Focused Core Clinical Outcomes Could Enable Labeling Comparisons” - *Pink Sheet*, 25 Nov, 2022.)





Jung Won Shin
Senior Editor

What's Keeping Korea From Adopting Decentralized Clinical Trials?

Digital, Medical Literacy, Hybrid Approaches Highlighted

The current status of decentralized clinical trials in Korea and the country's efforts to boost activity in this area were discussed at the recent Bio Korea meeting, with cultural and medical practices, along with technological and medical literacy, among the areas seen as affecting broader adoption of the various elements of the approach.

Decentralized clinical trials (DCTs) have been rapidly transforming the global clinical research environment by enabling faster recruitment through expansion of patient pools and the reduction of burdens for patient participation.

The various advantages of the approach were particularly highlighted during the COVID-19 pandemic, when it became difficult to enrol patients through standard means. However, in east Asian countries such as South Korea, adoption of the various elements of DCTs has been relatively slow.

During the recent 2023 Bio Korea International Convention in Seoul, experts shared views on the adoption status of such trials in Korea, as well as the country's efforts to boost use of the various components of DCT to catch up with the progress globally. They also highlighted the need to take into consideration medical and digital literacy, as well as a potential hybrid approach to DCTs.

FACE-TO-FACE PREFERENCE

Besides use in the rapid development of vaccines and drugs for COVID-19, DCT approaches have so far also seen adoption in trials for metabolic and rare disease drugs, given that it is generally difficult to recruit patients in these areas and to ensure diversity.

In Korea, however, reasons other than the regulatory environment have held back the progress of DCTs.

"Korea may be a small country, but it has a great public transportation system and patients largely gather at major hospitals where many clinical trials are conducted. And most of these patients

prefer to visit hospitals as they are more used to meeting physicians face-to-face for consultations to proceed with the study, even though it may be more convenient to do this at home," Jaeseong Oh, professor at the Department of Clinical Pharmacology and Therapeutics at Seoul National University Hospital told the conference, organized by the Korea Health Industry Development Institute.

"In Korea, patients tend to prefer face-to-face medical treatment and clinical trials. I think other East Asian countries also have such a tendency."

On the other hand, in the US it may take several hours by car, or even a plane ride, to visit trial sites within hospitals, a situation behind the more active adoption of DCTs there. It can also be difficult and costly to simultaneously recruit subjects from multiple hospitals in various states, another factor favoring DCTs to facilitate this, Oh explained.

Citeline's recent white paper, *Unlocking The Potential of Decentralized Clinical Trials*, showed regional differences when looking at the geographical landscape of trials with DCT attributes: Asian countries, including China, South Korea and even Japan, have been more resistant to pivot towards novel trial designs and are lagging behind.

As of February 2023, Korea's percentage of trials incorporating DCT attributes stood at just 1.5%, while Japan was 2.9% and China even lower at 0.5%.

In addition, Korea has never faced a full lockdown during the pandemic, when patients continued to visit hospitals and clinical trials did not see serious disruptions, although there were some delays because of issues in delivery and disruptions to patient monitoring as hospitals had to halt external visitors.

"Demand for remote monitoring has increased sharply in the country...if this was more smoothly handled, then clinical trials would have been managed better, in my view," Oh declared.

SOME ELEMENTS WIDELY ADOPTED

Nevertheless, some elements of DCTs have been more widely adopted than others in Korea. According to a survey by a DCT collaborative working group in 2021, digital data collection tools were the most widely implemented, while remote monitoring and sponsor visits to study sites, as well as direct-to-patient deliveries, were still quite limited. Other aspects, such as electronic informed consent forms and local lab use, were scarcely adopted at all.

Korea is seen as a country with strong IT technology, but when it comes to the medical environment, this doesn't appear to be transferring well because of regulatory issues or because patients and physicians may not prefer this, Oh said.

From a legal perspective, there are in addition still many issues Korea has to resolve, such as data privacy protection and the "credibility" of technology. The country also needs a direction in its relevant regulations, said Hyun Wook Han, professor of Medical Information, Bioinformatics, at CHA University.

As one example, telemedicine was allowed temporarily because of the COVID situation, but is set to end in May. The country is now looking to at a new pilot project following other previously over the years, but has still to make a final decision. If it is not proactive, it may lag behind others in DCTs, Han cautioned.

NEED TO CONSIDER DIGITAL, MEDICAL LITERACY

He also suggested the need to consider the state of digital and medical literacy in Korea when looking at DCTs.

"This is not only a medical issue. This is about digital literacy among all age groups and the medical literacy issue is even more serious. This is about terminology and accessibility. All the smartphones and IT infrastructure is created for average people, so 'digitally disadvantaged' people such as the elderly will have difficulty accessing them," the professor told Bio Korea.

"Other countries are already thinking a lot about medical literacy, while in Korea certain state research projects are being announced [in this area]."

DCTs also have to consider diverse ethnicities, ages, diseases and other humanistic factors and Han suggested engineers should take these into consideration when designing related software.

Oh additionally warned that fully replacing traditional trials with DCTs might raise issues around Good Clinical Practice and ethics and how valid and credible the data are. DCT elements have advantages but need to be harmonized, and "We need to plan DCTs by taking into consideration what elements will be adopted and how far will they be adopted from the study planning stages."

A hybrid approach may therefore be preferable. "From a scientific perspective, we can also see how much patients are engaged in this when we meet and explain to them. We can also provide more explanation so they have a better understanding."

MIXED ACTUAL IMPLEMENTATION

The Citeline white paper notes the actual incorporation of DCT elements is not in line with the extensive attention DCT designs are receiving. The number of trials incorporating one or more DCT elements has increased slightly, from 376 trials that started in 2016 to 526 starting in 2021. However, the vast majority of studies still do not incorporate DCT attributes, or at least there is no easily accessible public disclosure of this.

So real-world adoption appears to be low, despite the potential advantages to sponsors and patients of DCTs.

Sponsors are most likely to include DCT elements in later-stage trials, particularly Phase IV (post-marketing) studies on long-term risks and benefits, followed by Phase III. As Phase IV trials are typically longer in length, the need to continually visit sites becomes a greater burden, resulting in the use of DCT approaches, the white paper noted.



Korean Patients Prefer Hospital Visits, Face-To-Face Treatment.

Source: Jung Won Shin



Anju Ghangurde
Executive Editor,
APAC

Indian ‘Lighthouses’ Deliver Gains Amid Price Erosion, Rising Input Costs

Digital, Analytics & Automation Can Have “Breakthrough” Impact, Says McKinsey

Senior executives from Dr Reddy’s and Cipla showcase the “step-change” in performance across cost, quality and delivery metrics at their ‘lighthouse’ manufacturing sites in India as industry tackles dwindling operating margins and evolving compliance requirements.

Pharma may have traditionally lagged some other sectors when it comes to adoption of digital technologies more widely but manufacturing is one area where industry appears to be making important strides leveraging smart technologies and data-driven processes to deliver meaningful gains.

A recent conference in India heard how two frontline companies – Dr. Reddy’s Laboratories Ltd. and Cipla Limited – transformed their factories with the adoption of fourth industrial revolution

(4IR) technologies bringing about a “step-change” in performance across cost, quality and delivery metrics.

Both companies have sites accredited over the recent past as ‘digital lighthouses’ by the World Economic Forum (WEF) and join Johnson & Johnson, GSK plc, Bayer AG, Novo Nordisk, Sanofi and Teva Pharmaceutical Industries Ltd., among other peers that are part of a list of 19 pharma and medical devices firms which boast such facilities globally. Lighthouses essentially apply 4IR technologies at scale to drive financial, operational and sustainability improvements by transforming factories, value chains and business models.

Addressing the Global Pharmaceutical Quality Summit 2023, organized by the Indian Pharmaceu-

tical Alliance (IPA) in Mumbai, Vivek Arora, partner, McKinsey & Co, said that digital, analytics and automation has the potential to deliver “breakthrough” impact in life sciences operations.

These technologies could translate into as much as a 25-40% increase in overall asset productivity, a 30-50% jump in labor productivity, while in areas like quality excellence/improvement it could help deliver a 30-50% reduction in deviations and a 200%-plus increase in product robustness, data presented by executive indicated.

“Overall, the cumulative impact has been anywhere between 3-5% point improvement in profitability in the business being generated from the lighthouse sites,” Arora said.

Outside of the quantitative impact, it also helps free up the time of operational leaders from “non-value-added activities”, to spend “quality time” on the shop floor with their teams helping, coaching, problem-solving and driving continuous improvement, the executive added.

Arora highlighted some of the core themes that can unlock value with the adoption of a digital production system operating model. These include reimagining important shopfloor processes using automation, ‘digital guides’, artificial intelligence and augmented reality; no touch planning of all production and quality activities using digital twins; and using data and analytics to make products more robust, and reducing deviations, improving yield and critical quality parameters. (Also see “Re-Configuring Pharma Operations Amid Pandemic Strains” - *In Vivo*, 8 Apr, 2021.) (Also see “ChatGPT Unleashed: Generative AI Use Cases Taking Off In Pharma” - *Scrip*, 6 Jun, 2023.)

NOVEL WAYS TO IMPROVE PRODUCTIVITY

Senior executives from Dr Reddy’s and Cipla then went on to share more granular details on the large-scale digitalization efforts that led to the coveted lighthouse status for their sites amid growing challenges in industry alongside evolving compliance and quality expectations. (Also see “FDA’s McMullen: No Bigger Waste Than Drug Shortages Due To Data Integrity” - *Pink Sheet*, 27 Jun, 2023.)

Madhu Sundar M S, senior vice president and global manufacturing head (FTO), Dr Reddy’s Labs, referred to massive pricing pressures with rising input costs and increased competition as the backdrop against which the company embarked on its digitization journey. (Also see “Dr Reddy’s On Digitization Amid COVID-19, ‘Lights-Out’ Manufacturing” - *Scrip*, 19 Mar, 2021.)

Declining prices have hurt profits of generic firms in key markets like the US. Public earnings data of 24 generics firms in the US with the highest revenues, analysed by experts, has shown that the median ratio of earnings before interest, taxes, depreciation and amortization (EBITDA) to revenues declined from 24% in 2017 to 20% in 2022. (Also see “Why Generic Drug Manufacturing Is Faltering And Ways To Bolster It” - *Pink Sheet*, 2 Jun, 2023.)

“The dwindling operating margins in the US, the single largest market, is a wake-up call for the entire industry, to look for novel ways to improve its productivity, even as it stays the course on maintaining compliance,” Sundar said.

The company decided to digitally transform its largest and most important facility, FTO Unit-3, in Hyderabad, the largest revenue contributor from Dr Reddy’s formulations manufacturing sites but also one of the firm’s oldest sites.

“If you look at the infrastructure, it could stretch between the sublime to the ridiculous - we had some very old equipment and some very cutting-edge technology/equipment as well. Collecting data from each of this was going to be a daunting challenge,” Sundar said recalling the early days.

The plant, with an installed capacity of more than 10 billion units per annum, is licensed for production of 250-plus products including life-saving cardiovascular and gastrointestinal therapies. Importantly, FTO Unit-3 has 100% export volumes with over 65% of turnover contributed by sales in North America. It has been successfully audited by 15-plus regulatory bodies and supplies products to 25-plus countries.

Cipla similarly built a digital-automation-analytics-enabled network of 20-plus facilities in two years, led by its oral solid dosage (OSD) plant in Indore, which unlocked industry leading performance and went on to be designated as an



advanced 4IR lighthouse by the WEF.

“We started with setting a very bold aspiration for ourselves - to create plants of the future within Cipla that would rewire plant operations, upgrade technologies and reduce people dependence,” Geena Malhotra, global chief technology officer, Cipla, said in a video address at the summit.

The end vision is to develop a network of ‘touchless factories’ that can deliver best in class performance, Malhotra maintained.

DR REDDY'S 'OPS NEXT' STRATEGY

Dr Reddy's Sundar outlined how the company adopted its ‘Ops Next’ strategy at FTO Unit-3 putting into action a five-pronged approach to leapfrog into the ‘next phase of excellence’.

It entailed, among a range of activities, getting all the data in one place including in “some places on the plant, which have digital silence”, while also identifying 40-plus digital and advanced analytics use cases spanning six major 4IR technologies. It also required people and talent development to support change – recruitment, capability building and organizational restructuring. (Also see “India’s ‘Thousand Talents’ Moment And Models To Shift Gears In R&D” - *Scrip*, 24 Nov, 2021.)

Two interesting use cases saw the use of augmented reality and virtual reality around new operator training and for remote assistance for method transfer; in the latter sites situated several hundreds of kilometers away could do a virtual guided transfer with the R&D facility in Hyderabad. (Also see “GSK CTO, Boehringer Exec On The Metaverse And Pharma’s Foot In The Door” - *Scrip*, 9 Mar, 2023.)

The firm invested heavily in digitizing its operating system at scale, spanning aspects such as integrating peripheral data across 50-plus sources to create a single source covering 80% of all data and also connecting all the plant data sources to the data lake ensuring easy access to data.

The transformation brought ‘remarkable’ improvement in productivity metrics, Sundar declared. It resulted in a 43% reduction in manufacturing cost per 1000 pills; there was a 56% increase in factory output helping sustain margin against erosion of prices and a 30% reduction in production lead time. In terms of quality, it led to a 76% reduction in the incidents per production batch, while there was a 43% reduction in customer complaints due to improved process and execution robustness.

FUTURE-PROOF ENTERPRISE-WIDE DATA TECH BACKBONE

Cipla’s Malhotra similarly recounted how the digitization journey entailed setting up a future-

proof enterprise-wide data technology backbone for the firm’s analytics work across the network. The second aspect was to set up a digitally native organization by infusing new data science talent and upskilling existing teams to embrace a “new way of working”. (Also see “Respiratory Plus: Cipla Shapes Future In New Age Platforms, Devices, Diagnostics” - *Scrip*, 18 Jan, 2022.)

For instance, 1,000 plus users (operators and supervisors) were trained in the digital and analytics-enabled way of working, while 50-plus ‘champions’ - unit and site leaders - were trained on taking data driven decisions as part of efforts to upgrade existing roles.

Cipla went on to deploy more than 45 digital-automation-analytics use cases across its network. The company, for example, used predictive maintenance for equipment on constrained lines to trigger interventions before “major breakdowns”, while advanced analytics-led process simulation was also used to improve yield and process capability and deliver “golden batch” outcomes consistently.

Malhotra also pointed out that most machine operations are judgment driven, with significant reliance on the skills of operators, but with the use of advanced analytics, the company could make a deliberate shift towards data-backed, prescribed parameters for the machines, allowing the firm to unlock more than 30% manufacturing efficiencies in priority areas.

More specifically, the Indore OSD plant could unlock over 26% reduction in total cost of products manufactured at the site; 23% increase in people productivity; over 50% increase in in asset efficiency and more than 40% reduction in specific energy consumption.

DON'T INVEST FOR THE SAKE OF TECH

The Cipla executive, however, warned against falling into the “trap” of making investments just for the sake of digital adoption or digitization.

“Do not invest for the sake of technology. This journey is not inexpensive but real success comes when you take a strong value-backed view to any investment/initiative,” she said. For example, Cipla takes a very strong 24-30 month payback view of all the digital investments the firm has made, she added.

Malhotra also believes that over the next decade, there will be two types of businesses - one set of companies that could lead the market because they are using digital, advanced analytics and artificial intelligence in the regular manufacturing process, and others that haven’t adopted these technologies and could potentially either shrink or find it very challenging to remain competitive.



Brian Yang
Managing Editor

China Steps In To Help Relieve US Cancer Drug Shortages

Despite Wider Decoupling Underway



At least one major Chinese supplier is being tapped to relieve a shortage of certain drugs in the US despite rising Beijing-Washington tensions, but China may be increasingly unwilling to co-operate amid its own shifting economic priorities, increasingly introspective policies and some shortages of its own.

In early June, an announcement from the US Food and Drug Administration highlighted an urgent need to secure continued supplies of certain drugs. The agency noted that more than 130 products, including 14 treatments for cancer, were in short supply.

On 13 June 13, the Health Subcommittee of the US House of Representatives then held a public hearing to highlight the issue, during which it was reported that more than 90% of members of a cancer treatment network were experiencing shortages of chemotherapy drug carboplatin.

Already in a “Dear Healthcare Professional” dated 24 May, the FDA said it had been coordinating with Chinese firm Qilu Pharmaceutical Co., Ltd. and its US distributor, the major generic company Apotex Inc., to temporarily import quantities of another platinum-based cancer drug, cisplatin to help relieve the situation.

Qilu is one of the largest generics manufacturers in China and so the Jinan-based firm was in a good position to meet the US demand. However, whether its supplies will be adopted as a long-term solution remains to be seen amid ongoing geopolitical tensions and worsening bilateral relations.

The Chinese firm’s main focus is actually on

antibiotics, active ingredients and the manufacturing and supply of tablet preparations, it noted in its 2022 annual report released in April to the Shanghai Stock Market. This stated the company currently has 24 generics in development, with three abbreviated new drug approvals (ANDAs) and seven at the pre-ANDA stage. This portfolio includes anti-infectives, cardiovasculars and CNS drugs, as well as anticancers.

QILU SEIZES OPPORTUNITY

Most of the anticancers currently in short supply in the US are harder to manufacture injectables, in which Qilu is investing heavily and aims to become a major producer competing with Indian generics firms in the sector. The company is prioritizing injectables and biologics as a future growth pillar after generics and innovative new drugs.

The Shandong-based firm has submitted 13 generic injectables for bioequivalence testing, as required by Chinese regulators prior to ANDA approval, of which six have already obtained the clearance and six are in the pre-ANDA stage.

Qilu has the dominant share among the nine producers of cisplatin in China, helped in part by the Chinese government’s volume-based procurement policies, under which prices are slashed in exchange for promised volumes of public hospital orders.

The scheme is drastically changing the supply of drugs in China. Prior to its adoption, the market was highly segmented with many smaller players

- but now, it is effectively a “winner takes all” situation allowing big players like Qilu to supply the bulk of the market.

Other players in the cisplatin sector include Jiangsu Hengrui Pharmaceuticals and Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

‘DUAL CIRCULATION’ POLICIES

Viewing China as increasingly contained internationally by the US and its allies, Chinese President Xi Jinping wants to expand domestic markets to better cope with restrictions imposed on international trade by Washington and ensure continued economic growth.

Fuelled by geopolitical tensions, including over Taiwan, Hong Kong SAR and Xinjiang province in China’s west, Western governments are following the US in restricting technology exports to China, starting with high-end semiconductors. Beijing views the developments as just the latest tactic to constrain its global rise.

To counter this, Xi has been emphasizing a “dual circulation” economic policy, which distinguishes between domestically-driven and international growth. In a recent speech during a tour of Inner Mongolia, he said that China must develop its own national markets and that the dual circulation policy is intended to enable China to “survive on our own and become even better when others close doors on us.”

As part of this strategy, Chinese drug makers are being encouraged to export their products but also to prioritize and restrict exports in case of pressing domestic need.

PRICE CUTS AND SHORTAGES

China has also faced its own ongoing challenges with drug shortages. Due to aggressive price-cutting, some manufacturers have bailed out after winning supply bids, while some have even halted production due to complex production processes, thin profit margins and low demand.

In 2022, the National Health Commission issued a list of 109 drugs that were experiencing shortages, in a step it said was just for “monitoring purposes.” Some products, including serum albumin for snake bites, have now been put under a designated production mechanism, meaning they are not subject to centralized procurement and producers are required to continue manufacturing and supplying the market.

For those drugs on the list, there is a higher possibility that China will restrict exports to other countries; so far, however, chemotherapy products such as cisplatin and carboplatin have not been included.

Given the tit-for-tat responses from Beijing to

Washington’s restrictions on key technology exports, China could potentially also restrict exports of anticancer drugs, which has prompted the US Congress to hold a hearing on preparedness for such medical supplies.

INFLUENCE OF MONOPOLISTIC PRACTICES

Price-fixing, formation of anti-competitive alliances and other monopolistic practices are other factors that have contributed to drug shortages in China. On 28 May, the national anti-monopoly regulatory agency, the State Administration for Industry and Commerce (SAIC), imposed penalties on two drug firms alleged to have manipulated supplies to maximize profits.

From 2010 until this May, the two active ingredient makers - Yuanda Pharma and Shanxi Zhengdong Taisheng Pharma, whose sole distributor is Wuhan Huihai - were the only two manufacturers of active pharmaceutical ingredients for adrenaline injectables, which are included in the official list of products in short supply.

Yunda and Huihai were found to have effectively controlled the market and used their dominance to command higher prices. The SAIC confiscated illegal income of CNY149m (\$21m) from Yuanda and fined the company CNY136m, and confiscated CNY30.9m in illegal income from Huihai, on top of a fine of CNY41.2m.

WIDER ACTION NEEDED?

Chinese companies aside, some Indian firms including Aurobindo Pharma Limited are among those reported to have seen soaring sales from demand to meet the US shortages.

The US FDA has also allowed India’s Intas Pharmaceuticals Ltd. to export cisplatin, carboplatin and 14 other injectables, as well as 10 oral dosage form products, to the US despite a GMP import alert the agency placed on the company last year on the condition it complete a third-party review and testing of the products.

The biopharma area is one of those where the Biden Administration is encouraging re-shoring, but the current shortage shows this process may be time-consuming given the need to build up additional domestic capacity and infrastructure.

Using temporary Chinese supplies to meet pressing shortfalls might also not be a sustainable solution. During the hearing of the US Health Subcommittee, the Community Oncology Alliance, a non-profit organization, proposed that Congress instead fix fundamental financial problems within the US health system of discounts, rebates and price caps that it saw as causing the shortages of injectable generics.



Brian Yang
Managing Editor

Falling At The Start Line: Chinese Firms Face Multiple Commercial Challenges Beyond Price, Coverage

First-In-Class But Low Revenues

Sales of a global first-in-class dermatology drug that gained its first approval in China are falling well behind those of its overseas counterpart. In this case study, *Scrip* takes a deep dive into the multiple underlying factors determining success in the world's second-largest pharma market beyond pricing and reimbursement coverage, including complex hospital entry, dual channels and competition considerations.

Covered by the National Reimbursement Drug List? Check!

Priced to compete with formidable competitors? Check!

Product awareness among specialists and physicians? Check!

For a Chinese domestically-developed, first-in-class, topical non-steroidal treatment, and the first new drug for plaque psoriasis in 25 years, benvitimod - also known as tapinarof and WBI-1001 - encountered a surprisingly uphill battle to gain commercial success on its home turf. Meanwhile, its overseas counterpart has attracted large investment and enjoyed considerably more success.

Receiving its first approval globally from China's National Medical Products Administration in 2019, the therapeutic aryl hydrocarbon receptor (AhR) modulating agent was originally developed by a team including the founder of Shenzhen Celestial Pharmaceuticals Ltd. and a Canada returnee, Genhui Chen.

It first gained national attention back in 2012 when global ex-greater China rights were acquired from Toronto-listed firm Welichem Biotech Inc. by GlaxoSmithKline Pharmaceuticals Ltd. dermatology subsidiary Stiefel, in a deal worth up to \$230m. In 2018, GSK subsequently sold its ex-China rights to Roivant Sciences Ltd.'s dermatology operation

KEY TAKEAWAYS

1. There's much more to commercial success in China than just approval and launch; reimbursement is only among the first steps.
2. Nationally reimbursed drugs are not guaranteed to enter hospital formularies, which can be a time-consuming process.
3. Be prepared to deal with the impact of new DRG and DIP systems as they are rolled out.
4. Foreign competition continues to rise.

Dermavant Sciences Inc., in a transaction valued at up to \$330m.

In 2013, Welichem acquired from Celestial and Beijing Wenfeng Tianji Pharmaceuticals exclusive rights to WBI-1001 in greater China (China, Taiwan, Macau SAR and Hong Kong SAR). (Under the Welichem/Stiefel agreement for the remaining global rights, Stiefel also received the conditional right to acquire greater China rights at a future date from Welichem.)

Benvitimod was designated a National Key Pharma Innovative Project in China's 12th Five-Year Plan and hailed as an achievement showcasing the success of regulatory reforms that started in 2017 to encourage the launch of innovative new drugs in the country ahead of anywhere else.

Marketed as Symbiox in China, it logged sales of only CNY34.35m (\$4.87m) in 2022 and despite 15% growth from the previous year, the figure was anemic compared to the same active ingredient's performance outside China.

For its part, tapinarof was approved by the US Food and Drug Administration as Vtama in 2022; Roivant reported \$9.2m in net product revenue for

the product in its third quarter ended 31 December alone, noting there had been nearly 100,000 prescriptions since launch. The company invested around \$200m for the market roll-out with a dedicated 100-strong commercial team, targeting an estimated four million plaque psoriasis sufferers in the US.

PROMISING CHINA START

In China, everything had seemed to be on the right track for Symbiox. After a high-profile launch, the drug was included in annual discussions for possible inclusion in the National Reimbursement Drug List (NRDL). Meanwhile, both the product and Celestial were acquired by Zhonghao Pharma, a subsidiary of the domestic listed group Guangzhou Guanhao Pharma.

After agreeing to slash its price by 72%, benvitimid was included in the NRDL for two years of coverage. Priced at CNY138 (\$19.60) per tube of 1% ointment, it then seemed poised to gain market share given the drug's national attention, high-flying accolades and most importantly large medical need.

China has one of the largest patient populations with plaque psoriasis and atopic dermatitis, another indication currently under Phase III development in China. Plaque psoriasis affects a larger number of patients in the colder northern regions of the country and is estimated to affect eight million people in total across the vast nation, roughly double the size of the estimated US population.

Cortisone steroids and vitamin D3 derivatives had been the standard of care in China, but adverse events and high recurrence rates meant there was demand for newer alternative treatments.

Many dermatologists in major class AAA hospitals in China had taken part in the Phase I to III clinical studies with benvitimid, which has enrolled a total of 1,200 patients. Compared to LEO Pharma A/S's Dovonex (calcipotriol), the drug had demonstrated longer relief time and lower recurrence rate.

According to published Phase III results, at the end of 12 weeks, 50.4% of benvitimid patients achieved PASI75 (75% or greater reduction from baseline in the Psoriasis Area and Severity Index), significantly higher than the 38.5% in the calcipotriol group.

COMPLICATED HOSPITAL ENTRY

However, while inclusion in the NRDL offers the promise of higher volumes (at the expense of lower prices), it does not mean a new drug will automatically enter hospitals. Each province must also set its own reimbursement rate and incorporate the

product into provincial-level reimbursement lists, in a process known as "guawang" or "listing in the network."

Furthermore, even after a province has listed a drug, each hospital decides whether to include it in their formulary.

The underlying considerations are complex. Some hospitals have a fixed number of drugs in their formulary, so adding one means having to remove another and the decision also needs to go through an internal Medical Affairs Committee.

The formulary listing process can be both time-consuming and daunting. The committees hold very few regular meetings throughout the year and getting a consensus also requires persuasion and preparation.

On top of this, even after formulary inclusion, prescriptions are constantly monitored given there are limits to the ratio of drugs within overall reimbursement costs. To reduce excessive prescriptions, physician prescribing patterns are also monitored.

TWIN DRG/DIP ROLL-OUT

Nationwide roll-out into diagnosis-related group (DRG) and diagnosis intervention packet (DIP) schemes in China are other factors determining commercial success. In late 2021, the National Health Security Administration issued a three-year plan to roll out DRG to hospitals nationwide.

From 2022 to 2025, the goal is to have 90% of medical conditions and 70% of medical insurance covered using the DRG or DIP methods. After concluding that nationwide DRG implementation is not feasible, the regulator decided to use both DRG and DIP, noted Kelly Ke, founder of bizi LLC and NRDL+, a life science publication devoted to market access in China.

"In essence, the DIP provider payment system is less technically demanding than the DRG system and can be more easily expanded," Ke said in a 3 May note to clients. "The DIP system can better



represent actual clinical practices and resource utilization in a large and diverse country like China,” while “pegging price adjustments to the regional global budget helps safeguard the social medical insurance funds.”

The goal is to use “bundled payments” under the DRG/DIP framework to monitor reimbursement and payments and reduce excessive diagnosis and prescriptions.

On May 10, Beijing health authorities issued guidance to link DRG and bulk procurement mechanisms, targeting medical consumables for the first batch. Haitong Securities analysts noted in a 14 May note that the public payer’s intention to control medical costs is increasing.

DUAL CHANNELS

Meanwhile, China’s medical insurance agency has initiated a new channel along with hospitals for new drugs included in the NRDL since 2020; designated retail pharmacies can also dispense such products under this “dual channel” mechanism.

Simply put, the idea is to improve patient access to reimbursed new drugs, providing easier and more convenient (sometimes 24-hour) channels with reduced prices.

To benefit, patients must obtain a prescription from a physician designated by regulators, meaning that not only the hospital but also retail store pharmacists can issue prescriptions. The patient only makes a self co-payment and the pharmacy will process reimbursement.

While the dual-channel did put retail pharmacies on level ground with hospitals, as reimbursed prices are pre-negotiated, the drugstore cannot

add a margin. Also, to meet strict product tracking, storage, and distribution requirements, pharmacies must upgrade their information systems to qualify for the mechanism.

However, getting reimbursed new drugs into retail pharmacies remains a challenge and patients report difficulties finding particular drugs and even if it’s available a pharmacy may not be able to offer coverage due to a lack of processing equipment.

COMPETITION HEATING UP

So as can be seen, getting a drug priced and covered by reimbursement are just the first steps along the road to commercial success in China. This is quite a different story to development, as some Chinese companies are finding out the hard way.

As more innovative new drugs originated abroad continue to enter China, helped by lower regulatory barriers, competition in particular indications is also increasing. In the plaque psoriasis space, there have already been local approvals for Sanofi’s Dupixent (dupilumab) and Novartis AG’s Cosentyx (secukimumab), and both antibodies are also included in the NRDL, meaning discounted prices.

“When deciding which drug is to be put into a formulary and be prescribed, hospitals and physicians have to weigh multiple factors including treatment protocols for the condition, single-use cost and the drug expense ratio in overall expenditure, among others,” one former analyst who worked for IQVIA on drug reimbursement projects told *Scrip*.

While antibodies may have a treatment advantage, small molecules are usually priced lower and efficacy and safety data also play a role in prescription decisions, they added.





Dexter Yan
Senior Reporter

Chinese Biotechs Ascend Deal-Making By Partnering Up Claudin 18.2 Agents

The recent partnerships on Claudin 18.2-targeting agents between Chinese biotechs and big pharma have brought China innovation to a new phase that Chinese firms can be proud of, an executive from Keymed Biosciences, one of the Chinese biotechs involved in such deals, tells *Scrip* in an interview.

Chinese biotechs have entered a new phase of partnerships with big pharma companies, providing Claudin 18.2-targeting agents en masse for potential combo therapy with the world's best-selling PD-1/L1 therapies.

Hong Kong-listed Keymed Biosciences Inc. and Lepu Biopharma Co., Ltd. were the latest to close the loop. Through a joint-venture, the duo on 23 February announced an up to \$1.8bn licensing deal with AstraZeneca PLC for the global development and commercialization of CMG901, a Claudin 18.2-targeting antibody-drug conjugate.

Earlier, five other Chinese drug makers also pulled off licensing or joint development deals on the Claudin 18.2 target, including Sichuan Kelun

Pharmaceutical Co Ltd. with Merck & Co., Inc. on its ADC, LaNova Medicines and Transcenta Holding Ltd. with Bristol Myers Squibb Company on another ADC and a monoclonal antibody respectively, CARsgen Therapeutics with Roche Holding AG on another monoclonal antibody and Harbour BioMed with AstraZeneca on a Claudin 18.2/CD3-targeting bispecific antibody.

"That's something that Chinese biotechs could be proud of," Yanrong Zhang, CFO of Keymed, told *Scrip* in an interview on 28 February.

Zhang was optimistic about the prospects of foreign licensees of Chinese Claudin 18.2 agents making blockbusters from the PD-1/L1 combo regimen in HER2-negative gastrointestinal cancers.

"It will become splendid examples of successful collaboration between global big pharma and Chinese drug makers," Zhang said.

Merck's Keytruda (pembrolizumab), BMS' s Opdivo (nivolumab), Roche's Tecentriq (atezolizumab) and AstraZeneca's Imfinzi (durvalumab)



booked \$20.9bn, \$8.2bn, CHF3.7bn (\$3.9bn) and \$2.8bn respectively in sales in 2022, according to the companies' financial results. These anti-PD-1/L1 antibodies are indicated for various types of cancer worldwide.

The executive also noted that the high prevalence of gastrointestinal cancers with Claudin 18.2 expression in China has prompted Chinese companies to jump into the fray on the target.

As of the end of February, 45 Chinese pharma companies were developing a total of 64 Claudin 18.2-targeting candidates in preclinical and Phase I-II clinical stages, according to Citeline's Pharmaprojects. The candidates' modalities include monoclonal antibody, ADC, bispecific antibody and cell therapy.

“It will become splendid examples of successful collaboration between global big pharma and Chinese drug makers.”

- Yanrong Zhang, CFO of Keymed

The ranks are set to grow further after the Japanese pharma Astellas in 2022 announced positive results for its anti-Claudin 18.2 monoclonal antibody zolbetuximab for gastric cancer from Phase III clinical trials. (Also see “Astellas's First-In-Class CLDN18 Antibody Meets Phase III Gastric End-points” - *Scrip*, 22 Nov, 2022.) (Also see “Astellas Reports Second Phase III Win With Zolbetuximab In Stomach Cancer” - *Scrip*, 16 Dec, 2022.)

MILESTONE FOR KEYMED

Commenting on its deal with AstraZeneca, which is the first collaboration with a multinational giant, Zhang said that it is of “milestone” significance for Keymed.

“AstraZeneca is the best option (as a licensing partner) for us,” Yuchao Geng, Keymed's senior director of business development, said in the interview.

She explained that the British-Swedish multinational could not only bring Keymed's CMG901 to the world stage but is also well positioned to make the ADC a leader in the domestic market.

Notably, CMG901 is the frontrunner among all domestic Claudin 18.2-targeting ADCs to show safety and preliminary efficacy in a Phase Ia clinical trial in Chinese patients with Claudin 18.2-positive gastric and gastroesophageal junction cancers, according to the clinical data disclosed in January at the annual Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology.

OPPORTUNITIES FOR OTHERS

Additionally, it is not just large multinationals that have shown interest in the Claudin 18.2-targeting agents developed by Chinese companies.

Nasdaq-listed Elevation Oncology, Inc., for one, in July 2022 in-licensed Hong Kong-listed CSPC's SYSA1801 (EO-3021), an ADC candidate, with the exclusive rights outside of Greater China. In January, the US biotech said it would further focus resources on the candidate to advance it in clinic.

Although smaller US biotechs have limited financial resources versus big pharma companies, they will probably “cherish the opportunity” by in-licensing Chinese assets, Zhang said. Therefore, these companies will try to progress the clinical development of their China-originated Claudin 18.2 agents as quickly as possible and even to overtake the multinational competitors in this area.

“It's very likely that they will license more Claudin 18.2 agents from China,” Zhang added. “But there are still challenges ahead, like all other collaborations.”



Anju Ghangurde
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India Trials Scenario: Leaders From Novartis, IQVIA, PwC Signal Winds Of Change

Leaders from Novartis, IQVIA and PwC discuss the ground situation for trials in India as regulatory reforms, improved infrastructure and clinical expertise provide opportunities. Potential in areas like orphan diseases and tips for peer Amgen on getting trials going in India were among other highlights.

If you're entering India for clinical trials, then don't do it half-heartedly, just 'go all in', but be careful about the initial choice of disease areas – that's the advice Novartis's head, global clinical operations, Badhri Srinivasan had for his peer at Amgen, Inc. which appears to be evaluating opportunities in the world's most populous country.

Responding to a question from Amgen's senior vice president, global development, Rob Lenz at a recent summit, Srinivasan said that while a number of companies have dipped their toes in the waters, "going in there and saying this is what we come into India [for] and this is what we need from India would be very powerful, but also really get the machine cranking". Novartis, for one, has

over four dozen trials underway in India and seems set to keep the momentum going.

Nonetheless, Novartis's clinical operations head also suggested that companies need to be selective about the disease areas targeted initially – choosing a disease segment that is perhaps "better done outside India" and then bringing it to India may result in "difficulties".

"That may reflect poorly on India. Do your feasibility work carefully, and then go into those areas in India with full gusto," Srinivasan told Lenz at the USA-India Chamber of Commerce (USAIC) Annual Biopharma and Healthcare Summit.

Srinivasan's general assessment and Lenz's interest are noteworthy, given India's ongoing efforts to lift its clinical research segment out of a trough via a slew of regulatory reforms, improved infrastructure and growing clinical expertise. The attention of big pharma sponsors perhaps suggests that things are headed in the right direction. (Also see "Foreign Firms Not Fatigued In India, Game For 'New Things'" - *Scip*, 28 Mar, 2022.)



“

We've seen the maturity of science in India - they're able to handle complicated protocols and ever more demanding disease management. We've also seen the maturity of hospital systems, the embedding of ICH GCP.”

- Badhri Srinivasan,
Head of Global Clinical
Operations, Novartis

The Novartis executive outlined how the company is looking at India as a “strategic location” given the Swiss group’s wider thrust into orphan/rare diseases, areas with high disease burden and the increasing need for diversity and inclusion in clinical trials.

“As we speak, we actually have somewhere like 55 trials going on in India; we have over the course of just the last few years recruited over 10,000 patients in India,” Srinivasan, a member of both the Global Leadership Team and the Innovation Management Board of Novartis, said at the summit.

Besides, with instability in various geographies around the world, “India has stepped in. A large portion of the gap has been filled by India,” he added, seemingly alluding to the disruptions faced by industry against the backdrop of the Russian-Ukraine conflict.

Other big pharma sponsors like Johnson & Johnson, with a “large book of work” in the war-torn region, had previously similarly highlighted opportunities for India as it seeks to shift trial activity elsewhere around the world. (Also see “India Trials

And Tribulations: J&J, IQVIA Execs Offer Potential Solutions” - *Pink Sheet*, 7 Jul, 2022.) (Also see “Parxel Execs On Global Adjustments In The Trial Site Landscape” - *Scrip*, 11 Dec, 2022.)

HANDLING COMPLICATED PROTOCOLS

Srinivasan also highlighted India’s role across the “full spectrum” of clinical trials for Novartis; the company also increasingly sees clinical trials as a “care option” for many patients.

“Right from protocol writing to clinicians to data managers, regulatory specialists, our technical R&D team, as well as medical writers, submissions - we handle a lot of our submissions, including things like ADCOMs [advisory committees] and stuff like that from the [US] FDA from India,” the executive explained.

Novartis has a significant presence in Hyderabad in India, with over about 2,400 personnel in just the development unit there.

“We’ve done that because we’ve seen an improvement in the regulatory landscape, we’ve seen the maturity of science in India - they’re able to handle complicated protocols and ever more demanding disease management. We’ve also seen the maturity of hospital systems, the embedding of ICH GCP,” Srinivasan said.

STREAMLINED APPROVAL PROCESSES

Clinical trial activity in India had been tepid over the past several years, amid uncertainties and delays caused by evolving regulations at the time (many aspects of which have since been addressed) and past trial-related public interest litigation, among other factors.

But things have changed significantly since. A report by PwC India and USAIC suggested that some of the historical perceptions about conducting trials in India no longer stand.

Regulatory reforms post 2013 and the seminal New Drugs and Clinical Trial (NDCT) Rules of 2019 have streamlined the approval processes, reduced the timelines by 30-40%, and introduced several exemptions and provisions to improve the overall efficiency of conducting clinical trials, it noted.

Top 20 pharma sponsored trials in India rose 10% since 2013 following multiple regulatory reforms, the report said, though the country’s contribution to global clinical trials averaged at about 4% per year from 2010 to 2022 despite its large population base. (Also see “ISCR’s Davis On Pandemic Adaptations, Value Of Multi-Regional Trials” - *Scrip*, 26 Apr, 2021.)

Nevertheless, there are encouraging signs overall. A Citeline white paper in 2022 noted how the Asia Pacific region had seen trial activity trending upwards over the last decade - the region con-

CLINICAL TRIAL OPPORTUNITIES IN INDIA

The PwC India-USAIC report on “Clinical trial opportunities in India” delved into details around the perceptions, the risks, progress on ground and distilled how much of the narrative around the trials scenario is real and of concern.

PwC’s Leader, Global Health Industries Advisory, Sujay Shetty, noted that India’s clinical trial journey has been rather ‘more down than up’ over the last decade due to a number of reasons driven by several ‘self-inflicted wounds’ and some regulatory issues, though things are changing.

“The time is good now. It’s been through its ups and downs but there’s been a significant improvement in the regulatory climate and infrastructure, not to say it’s not without its concerns, but there’s been a lot of action, a lot of work on the ground that mitigates several of those risks,” Shetty said at the USAIC summit.

The report outlines how top biopharma firms can develop a long-term portfolio strategy targeting Indian sites and participants. This includes adopting a “portfolio-based strategy” that targets therapy areas with high prevalence in India (e.g., diabetes, CVD, oncology) and low recruitment rates in the US; building a network of partners such as investing in forming a therapeutic area-based network of partnerships and collaborations with public and private sector hospitals, research institutes, and advocacy organizations and; pursuing “niche busters” which could include accessing India’s large rare disease patient pool and enabling ecosystem strengthened by the establishment of public and private sector CoEs (centres of excellence) for rare diseases treatment.

Scrip had earlier reported how Roche, for instance, has partnered with the Indira Gandhi Institute of Child Health, Bengaluru, one of the CoEs for the diagnosis and treatment of rare diseases in children in India.

Some of the Swiss group’s other partnering initiatives are with the not-for-profit Extension For Community Healthcare Outcomes (ECHO), Prasanna School of Public Health and Karunashraya to launch a community level upskilling program for primary health doctors to help detect rare diseases early in the community amongst patients presenting at the primary healthcare centers in Karnataka. (Also see “New Hope, Funding Approaches As Roche Brings Evrysdi To India” - *Scrip*, 2 Aug, 2021.)

tributed almost half of the entire global clinical trial activity in 2021. Strikingly, 10% of Asia Pacific trials included an Indian site, the data on the trial landscape in the Asia-Pacific region from 2012 to 2021 suggested.

Back at the USAIC summit, Dr Cynthia Verst, president, design and delivery innovation, R&D solutions, IQVIA, referred to a “very positive influence” of India’s NDCT regulations, wherein trial startup timelines in the country are now “very comparable” with those in other key regions.

These timelines, regulatory approvals on average, about 100 days, are very similar to those with the timelines of other countries like the UK, Bulgaria among others, Verst noted at the session on clinical trials.

The PwC India-USAIC report, released at the summit, pointed out that India’s Central Drugs Standard Control Organisation (CDSCO) now has 90 days to decide whether to approve global clinical trial applications versus the perception of “long clinical trial approval timeline of 120 days”. (See box on other details of the report)

The report also noted how orphan drugs can be exempted from both phase III and IV clinical trials in India versus the myth that there are “no incentives” for conducting orphan drug studies. While India doesn’t currently have a formal accelerated regulatory pathway in India for rare diseases, the NDCT, 2019, provides for a possible waiver of local clinical trials. (Also see “India’s New Trial Rules Tick

Right Boxes, Shed Interim Compensation Clause” - *Pink Sheet*, 31 Mar, 2019.) (Also see “India Tweaks More Trial Rules But Can It Change The Narrative?” - *Pink Sheet*, 5 Aug, 2016.)

The Subject Expert Committee (SEC), which advises the Indian regulator on trial-related permissions and approvals, decides if the waiver should be applied or not. Roche’s Evrysdi (risdiplam), for example, could hit the Indian market within 10 months of the US launch given the “very short” approval time, the unmet need and “willingness” of the CDSCO to make the drug available to patients fast, as the company put it at the time.

The Indian government machinery too made clear at the USAIC summit its intent to ensure a conducive environment for clinical research and the wider biopharma sector as a whole. Dr Vinod Paul, member of India’s NITI Aayog, a government policy think tank, said that India remained committed to making the country a hub of “ethical clinical trials” and also aims to enable industry’s efforts to work towards discovery of new molecules, use cutting edge technology, gene-based therapies and CAR-T cell therapies.

“We look forward to hearing from you on what other pathways must be innovated because these are different technologies/solutions and therapies; we’ll be happy to work with you to see how for those cutting edge technologies, further modification of the regulatory system should be undertaken,” Paul said at the summit.

DATA QUALITY

Importantly, there were no overarching niggling concerns around data quality from India either, with panelists at the USAIC summit noting no material differences on that front versus global data sets.

“For us, we do not see a difference in data quality coming out of India; data timeliness is just as good coming out of the sites in India,” Srinivasan asserted at the session moderated by Takeda’s president of R&D, Dr Andrew Plump. (Also see “Big Pharma R&D Chiefs On IRA’s Unintended Casualty, Product Life Cycle Compression” - *Scrip*, 15 May, 2023.)

The Novartis executive also referred to expertise in India to handle more and more cutting-edge systems for data with not just not just CRF [case report form] instruments, but also devices.

“So the data science maturity actually helps in the clinical trial-handling maturity as well,” he declared.

IQVIA’s Verst pointed out that industry data on quality, and namely through the US FDA inspection data, actually reflect quality of India sites is not materially different from global site findings.

In fact, going by IQVIA datasets, “we’re finding very similar quality findings” when metrics like GCP compliance, protocol deviation and other parameters are considered, she said.

“We’re finding those data sets very comparable to global findings and pan-Asian findings”.

Dr Naresh Trehan, chairman of the multi-specialty institute, Medanta - the Medicity, emphasized that integrity of data depends on “who you engage with”, highlighting how institutions such as his in India are accredited by the US, Joint Commission International (JCI), the highest accreditation for quality healthcare and has other accolades come its way over the years.

“That didn’t happen because we don’t have the

sanctity of the data and the work we do. These examples apply not only to us but many other institutions - government and other private ones. So, we value our reputation, we value our data/the research that we do and the outcomes we have, because we are the beneficiaries or the victims of it,” asserted Trehan, a leading cardiovascular and cardiothoracic surgeon.

“So, one thing the world should be very clear about is that the [clinical research] landscape [in India] has changed for the better.”

CHALLENGES REMAIN

The generally improved outlook for trials in India notwithstanding, there still are areas of concern that need to be addressed.

Novartis’s Srinivasan sought continued improvement “in the ability to start up trials in India and continued streamlining of the regulatory landscape along the lines of improvements already done” but also flagged up talent management in clinical trials as a huge area of concern.

“What can we do as India, as companies in India such as ours to ensure high quality talent that results in high quality clinical trials as well?” the executive asked.

The PwC India-USAIC report said that the availability of investigators in India had doubled between 2015 and 2020 in the top pharma sponsored trials in India. Five Indian states - Maharashtra, Tamil Nadu, Gujarat, Delhi, Karnataka - accounted for 65% of all investigators, with 20% of investigators specializing in internal medicine, followed by oncology (11%), endocrinology (7%), gastroenterology (6%), and cardiology (5%), data in the report indicated.

IQVIA’s Verst said that a key challenge conveyed by sponsors across large, mid-tier and even emerging biopharma is the “whole notion” of the ‘intent to market’ in India.

“So essentially, the regulations highlighting that sponsors wanting to include India in clinical trials, that they are committing to commercializing the product,” Verst stated.

Related to the intent to market/commercialization component, Verst has in the past flagged the need to address requirements around having a specific percentage representation of the Indian population for certain clinical studies and also a mix of public versus private investigator sites in the country.

Intellectual property protection continues to be another area of concern, though the intensity appears declining. Verst maintained that concerns around IP issues, as a proportion of launch considerations, has declined from 15% in 2006-2012 to less than 5% in 2013-2021.





**Anju
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Eye On ROI: Will More Indian Firms Re-Calibrate US Market Presence?

Could more Indian firms consider re-aligning their US business amid heightened pricing and compliance pressures that have cast a shadow on the long-term viability of the generics segment? A cross section of experts including a senior executive at McKinsey & Co share their views on what to expect.

Indian pharmaceutical firms are seen re-calibrating their strategy for the US market in an increasingly competitive environment aggravated by price erosion and the growing cost of compliance.

While it's not as if some sharp exodus is in the offing, but there's a shift away, at least at some firms, from an "almost single-minded focus" on the US market, as one industry expert put it.

"There is a very conscious focus on return on investment at a geographic market opportunity level," said Vikas Bhadoria, McKinsey & Company's senior partner at a recent roundtable discussion on the eve of the Global Pharmaceutical Quality Summit 2023 in Mumbai.

While drug makers that operate in markets like the US understand fully well what the "cost of

quality" is – a warning letter/import alert could set firms back sharply – they also need to factor in investments in building capabilities/upgrading sites as also Generic Drug User Fee Amendments (GDUFA) fees. (Also see "FDA's McMullen: No Bigger Waste Than Drug Shortages Due To Data Integrity" - *Pink Sheet*, 27 Jun, 2023.

"So, then the question is - is it worth it to be present in the US market? That's the question that comes in, because there's a lot of investment that goes in and with the pricing pressure that exists, that is a real choice that people are grappling with at an individual company level," explained Bhadoria who leads the global management consultancy's Life Sciences Practice for India and the Pharmaceutical and Medical Products (PMP) Operations Practice in Asia.

In FY 2022, the US Food and Drug Administration had net collections of \$546m in human generic drug user fees, while firms that are part of the Indian Pharmaceutical Alliance (IPA) are said to have contributed around \$100m in such fees.



US CUTBACKS

There are already some signs of re-calibration of the US business by Indian firms driven by a range of reasons – Alkem Laboratories Ltd, for instance, has opted to “discontinue” its plant in St. Louis, which was meant for controlled substances due to the “structural changes” happening in the US market, while Torrent Pharmaceuticals Ltd. had earlier pulled the plug on its liquids business there. (Also see “Glenmark Chief: Running A Facility In The US Has Been A Struggle” - *Scrip*, 31 May, 2022.) (Also see “Torrent Acquires Chronic Brands From Dr. Reddy’s, Folds Up US Liquids Business” - *Scrip*, 27 May, 2022.) (Also see “Lannett To Close And Sell NY Liquids Plant As Part Of Restructuring Plans” - *Generics Bulletin*, 8 Nov, 2021.)

Earlier this year Goldman Sachs referred to Alkem’s ‘aspiration’ to maintain current revenues (rather than focusing on topline growth) as it strives to turnaround the US business margins in fiscal year 2024. The company also referred to “not allocating any more capital to the US generics business,” Goldman Sachs said in a report in March.

In the case of JB Chemicals & Pharmaceuticals Ltd., the report highlighted that the firm does not intend to enter the US generics market as a front-end player and expects to pursue its “cost plus” model which it believes can continue to deliver double digit growth in FY24. *Scrip* could not immediately verify if there has been any change in Alkem or JB Chemical’s stance since.

Another firm Wockhardt Limited said it was restructuring its US business given the “significant amount of drain into the financial performance of the company”. The revamp included a shutdown of the firm’s manufacturing facility at Morton Grove near Chicago, with few high margin products expected to be manufactured by a third party.

“As a result of the entire restructuring of the

manufacturing, we intend to save about \$12m in losses which we are currently incurring; however we will continue to maintain our sale in the US business as these products will be manufactured from a third party certified facility with approximately 40% gross margin,” Wockhardt’s senior management said earlier this year.

CONCERNS AROUND ECONOMIC VIABILITY OF GX

Such cutbacks or cautious approach comes amid a wider discussion around the “diminishing” economic viability of the generic pharmaceutical industry, which in turn has contributed to supply disruptions and drug shortages in the US.

A study by Anthony Sardella, senior research advisor at Center for Analytics and business insights adjunct professor, Olin Business School, Washington University, earlier highlighted how price erosion exceeded 50% since 2016 and is further accelerated by the market consolidation of the number of drug wholesalers and group purchasing organizations in the US. An average high-volume 30-count tablet bottle of medicine is now less than \$1.50, the equivalent of 5 cents per tablet. (Also see “Why Generic Drug Manufacturing Is Faltering And Ways To Bolster It” - *Pink Sheet*, 2 Jun, 2023.)

Declining prices have scraped off profits of generic firms materially. Sardella’s analysis of the top 24 generic companies by revenue over the past five years pointed to a “rapid degradation” in earnings due to these price pressures - all top manufacturers saw earnings decline since mid-2021, while the bottom quartile had fallen below a 15% operating profitability ratio.

“The implications of such economic indicators can be dire: reduced earnings will lead to cost-cutting and a reduced ability to invest in new product development, factory maintenance, overheads, technology innovation and investment in quality systems,” he asserted.

The academic researcher also highlighted the trend in addressing FDA manufacturer warning letters which fell from one-in-four warning letters closed out to one-in-20 by 2022. One of the drivers for the declining trend of closing out compliance issues is the high cost to address compliance and quality challenges relative to the low profitability, he claimed.

The Association for Accessible Medicines (AAM) recently added its voice to the discussion around drug shortages in the US and the sustainability of low-cost generic manufacturing, while seeking faster resolution of regulatory issues like quality problems among other aspects.

AAM referred to decreasing generic prices, how drug purchasers are becoming more concentrated,

new generics are not adopted as quickly while some generics are never launched given the limited commercial opportunities, and registered manufacturing sites are on the wane. "These changes force generic manufacturers to reconsider production of lower-margin, often older, medicines to ensure continued financial sustainability of the overall pipeline. Generic product discontinuations have numbered over 3,000 since 2010 and appear to be on the rise," AAM said.

COMBINATION STRATEGIES

McKinsey's Bhadoria went on to highlight three broad approaches that Indian companies are using as they assess the challenging US landscape for generic medicines.

One set of companies, he said, could opt to stay put and continue in the US market noting that pricing is down but will recover over time and there are opportunities around individual molecules or shortages etc. Another set of companies, though, may well feel that the "US is very difficult; the cost is too high - it's prohibitive" and could hence decide to focus on Europe, emerging markets (EMs) etc.

A third set of Indian firms will likely double down on the opportunities in India, where they understand both the market and the stakeholders but have so far been focused on pharma but now expect to play in the broader healthcare spectrum. That could include expanding into areas like diagnostics and medical devices, among others.

"If you take individual Indian companies, you will see some combination of these three strategies. Somebody is doing US plus broadening in India, somebody is doing Europe, emerging markets

and broadening in India. So, some combination of these strategies is playing out," Bhadoria pointed out. Industry, though, has its eye firmly on ROI at a geographic market opportunity level, he stressed.

"RE-DISCOVERY" OF THE INDIAN MARKET

Industry experts appeared generally aligned with the strategic approaches or then some adaption of the models that Bhadoria outlined – a recalibration is on the cards or underway, they said but emphasized that the US market will stay critical to drive growth for most frontline Indian firms.

Utkarsh Palnitkar, founder and managing partner of Aarna Corporate Advisors, said that while the US market continues to be challenging from a competition and pricing standpoint, its sheer size in value terms will continue to make it an important part of the total business of most large Indian players.

Many players, he noted, have adopted a multi-pronged approach. On the one hand, is the top line- focused market widening approach, through new product launches, while simultaneously focusing on being cost competitive.

"On the cost front, a number of initiatives are already underway. The pre-dominance of the US in the total volume of business for large players will certainly be tempered, with almost a "re-discovery" of the Indian market. Dr. Reddy's Laboratories Ltd. being a case in point," Palnitkar, a former partner and head (infrastructure, government and healthcare) at KPMG India, told *Scrip*. (Also see "Dr Reddy's Wants To Break Into Top Five In India" - *Scrip*, 18 Jan, 2021.) (Also see "Dr Reddy's CEO: We're In 'Great Dialogue' With The Innovation

STOCK MARKET PERSPECTIVE -US GX BUSINESS

From the stock markets perspective, experts signaled "some positivity" emerging towards the US generics business.

"To some extent the stock prices of Glenmark, Lupin and Aurobindo Pharma Limited over the last three months seem to demonstrate that. These stocks have given 25-30% returns over the last 60-90 days," Navroz Mahudawala, managing director of Candle Partners, told *Scrip*.

The seasoned investment banker said that to some extent the positivity was being driven by the "consistent performance" of Sun Pharma in the US and the positive outlook. Sun's formulation sales in the US (including Taro) for fiscal year 2023 (i.e. the 12-months ended 31 March 2023) stood at \$1.68bn (+10.3%).

"We do not expect any exits by mid and larger Indian companies. However we do expect recalibration of future investments. This is definitely being driven by review of return on capital employed (ROCE) across geographies and the fact that Indian markets have potentially given the best ROCEs," Mahudawala added.

He does not expect some of the diversifications into areas like diagnostics or nutraceuticals to create "any material topline impact in the near term", though.

A study by Candle had previously indicated that the Indian pharma sector had reported revenue growth of 7% over the last five years and attributed the flat/negative growth for the US businesses of several companies in the study universe as the single biggest contributor of the low growth rates. (Also see "Why India Pharma Failed To Impress In 2020-22 Bull Run" - *Scrip*, 5 Sep, 2022.)

Industry In China" - *Scrip*, 26 May, 2023.) Palnitkar, however, cautioned that venturing into other areas [in India], which are seemingly adjacent is 'fraught with danger', unless commensurate managerial bandwidth, and an operating model is put in place.

"Nutraceuticals is like a direct-to-consumer business, where brand building, sustained advertising and promotion is key. With the younger generation, increasing inclined towards wellness, the market potential does exist, however, the entry barriers are low," Palnitkar added.

Several frontline firms including Dr Reddy's, Lupin and Cipla are straddling business opportunities in allied areas such as nutraceuticals, diagnostics and consumer wellness on home turf alongside the core pharma business.

OTHER MARKETS CAN'T COMPENSATE FOR THE US

Other industry pundits were more emphatic, highlighting that opportunities in the US far outweigh other markets, at least for leading Indian drug makers.

Salil Kallianpur, a former executive vice president at GSK plc in India told *Scrip* that the US opportunity, while presenting headwinds, is still material and companies will find it difficult to "compensate for losing that big a market" by diversifying into the EU/EMs or into other categories such as nutraceuticals in the domestic market.

"Those markets while very lucrative, cannot come into play as an ex-US strategy; growth for Indian companies without an active participation in the US market will be difficult to achieve," declared Kallianpur who now runs a digital health consultancy.

The executive also explained the headwinds that Indian pharma faces in the US weren't unexpected and industry has spent the last few years preparing for it. Price spirals are led by increasing genericization and companies have over time responded by diversifying from vanilla generics towards more specialized and difficult-to-make products like

inhalers, transdermal patches and biosimilars.

"This has created niche opportunities for players like Sun Pharmaceutical Industries Ltd. Glenmark Pharmaceuticals Limited, Lupin Limited and Dr. Reddys. The emergence of [Mark Cuban's] Cost Plus Drugs and other such alternatives is filling in the gap that Indian players are exiting. It won't take long for these manufacturers to get into biologics and other niche products as well, but if Indian players have prepared well, they can still hold their own," said Kallianpur.

The larger issue, though, he maintained is the commitment of domestic players to quality and innovation in manufacturing "which still seems a way off". (Also see "Quality Street: India Needs A Frances Kelsey, Many Of Her Kind" - *Scrip*, 7 Jul, 2023.

Therefore, recalibration is definitely needed, he pointed out, but not only in looking for other markets (EU, Canada, China etc) where he reckons headwinds will be stronger than that in the US, but also by identifying the "right products and therapies to play in."

'MINUS-US' STRATEGY SEEMS TEMPORARY

Kallianpur further stated that Indian companies could consider a 'minus-US' strategy essentially for two reasons: either they are mid-size firms without a diversified portfolio or an organization that doesn't have a strong enough presence in the US or then these companies are better poised to tap into the double-digit growth in India through a combination of portfolio diversification in quasi-OTC (over-the-counter), non-Rx categories and/or rural expansion to tap greater growth.

"Either way, the 'minus-US' strategy seems temporary. The size of the market is so attractive that companies will continue to look at the opportunity waiting for the current trends to change," the executive specified.

The former GSK executive also highlighted another dimension touching upon the US Inflation Reduction Act, now facing multiple legal challenges.

The jury is still out on the IRA with lawsuits questioning its constitutional validity, Kallianpur noted also referring to the pharma lobby in the EU, which is likewise pushing hard against price negotiations and drug reforms brought in those countries as well. (Also see "PhRMA Teams With Provider And Patient Groups In Suit Against IRA Filed In Texas District Court" - *Pink Sheet*, 21 Jun, 2023.)

"Eventually, we might see watered-down versions of those legislations being implemented which may benefit generic manufacturers with significantly lower cost bases like Indian companies," he stated.

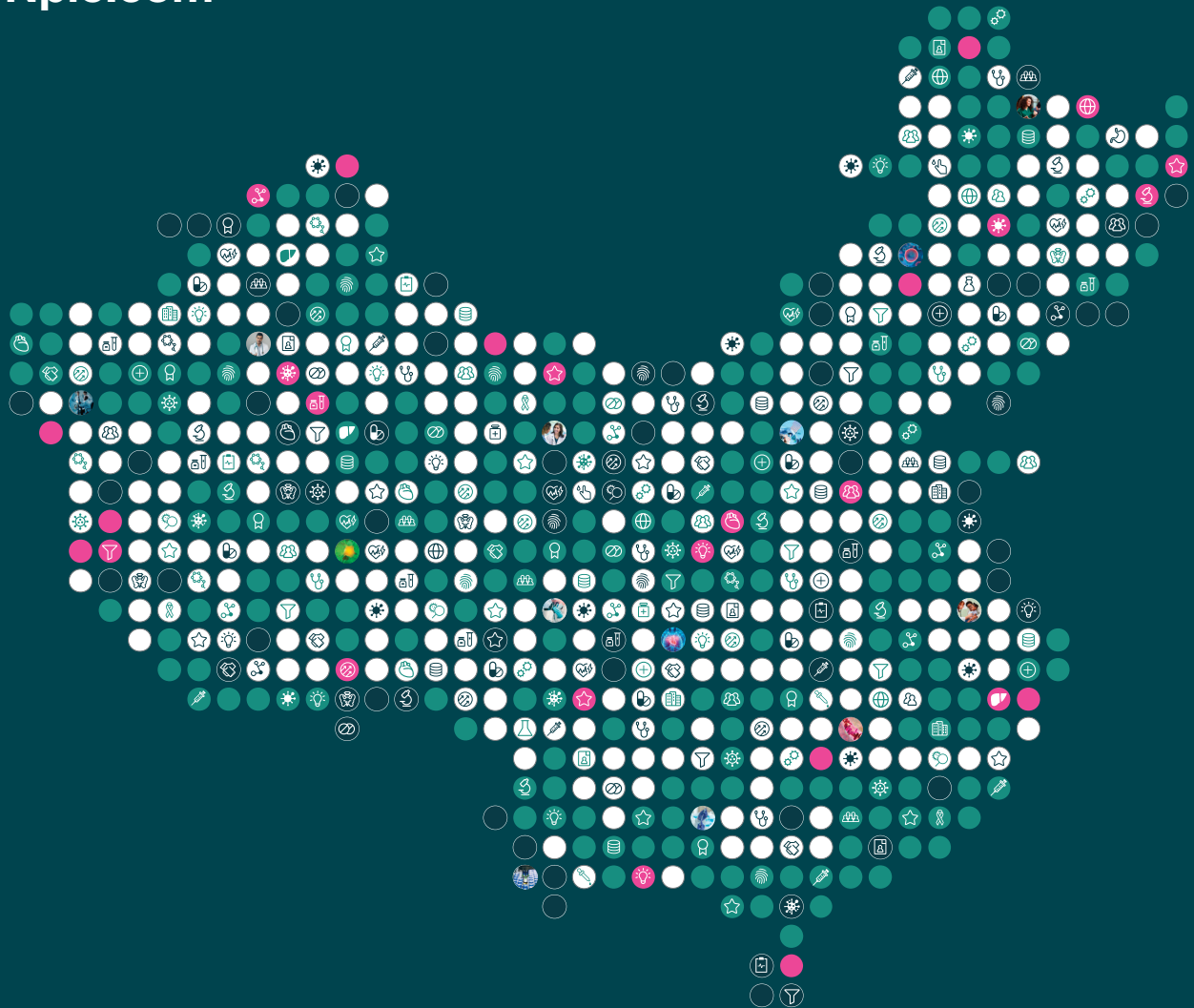




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Lisa Takagi
Managing Editor,
Japan

What's Behind Japan Firms' Higher Approval Rates In Challenging Oncology, CNS Areas?

Alliances Play A Key Role

Despite a global tendency for lower than average success rates from Phase I to approval in the challenging oncology and CNS areas, a recent Citeline study finds top Japanese pharma firms have relatively high rates in these two categories in the US. So what are the factors driving those differences?

The top 11 Japanese pharmaceutical firms have relatively higher R&D success rates in the US market in the areas of oncology and central nervous system (CNS), a new report from Citeline's *Biomedtracker* finds.

The research tracked past records for Phase I-III trials, revealing several major companies from

Japan including Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Takeda Pharmaceutical Co. Ltd. and Otsuka Holdings Co., Ltd. achieved higher-than-average likelihood of approval (LOA) rates from Phase I across oncology, CNS and rare diseases.

Facing ever fiercer competition and growth challenges in their home market, many large Japanese pharma firms have long prioritized developing a strong position in the US, which is now the most important market for a number in revenue terms, including Takeda. Several also have strategic alliance deals with western partners, the report points out.

HIGHER LOAS IN ONCOLOGY AND CNS

The report, "Probability of Success in Products Developed in the US by Key Japanese Pharma Companies", investigated both LOA and the probability of success (*POS; see footnote below for detailed methodology) at each phase of clinical development for the 11 firms: Asahi Kasei Pharma Corporation, Astellas Pharma, Inc., Daiichi Sankyo, Eisai, Kyowa Kirin Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Ono Pharmaceutical Company, Ltd., Otsuka Holdings, Shionogi & Co. Ltd., Sumitomo Pharma Co., Ltd. and Takeda.

The benchmark LOA value determined from all firms in the US market from the Phase I stage was 8.6%. However, the average LOA for the 11 Japanese firms was lower at 7.6% and also well below the average of 9.3% for the global top 15 firms, including Pfizer Inc., Roche Holding AG and Novo Nordisk A/S.

However, in oncology, the 11 Japanese firms had an LOA of 6.3%, above the average benchmark of 5.7%, with particularly high rates for Daiichi Sankyo (12.8%), Eisai (12.1%) and Takeda (7.3%). In CNS, the broader average was 2.1%, but for the surveyed Japanese firms the figure was 8.6%; it was especially high for Eisai (20.5%) and Otsuka Holdings (19.1%).

These two categories of oncology and CNS "typically have lower LOAs and POSs compared to all indications," Zhyar Said, the author of the report and a senior analyst for *Biomedtracker*, told *Scrip*, noting that pharma firms outside the US have "had a more difficult time attaining approvals for their US-based developments."

He added "This may have been due to different patient populations being treated in comparison to what is required for a US approval. I wanted to see if this was still the case even within the larger companies in an established country like Japan."

It was another surprising discovery for the author that the LOA in rare diseases for the Japanese firms (10.7%) was higher than that for non-rare diseases (6.6%). "This may be due to the fact that in Asia, Japan, South Korea and Taiwan have established systematic economic and regulatory incentives to encourage R&D of drugs for rare diseases," Said observed.

Japan has several well-developed schemes such as orphan and "Sakigake" (pioneering therapy) designations for innovative drugs, although these systems do not provide market exclusivity. Japan's orphan scheme provides advice on clinical trials, along with tax measures, priority reviews and a 10-year reexamination period. (Also see "Big In Japan: Assessing Seven Years Of Sakigake" - *Pink Sheet*, 27 Sep, 2022.)

STRATEGIC ALLIANCES BEHIND GLOBAL SUCCESS

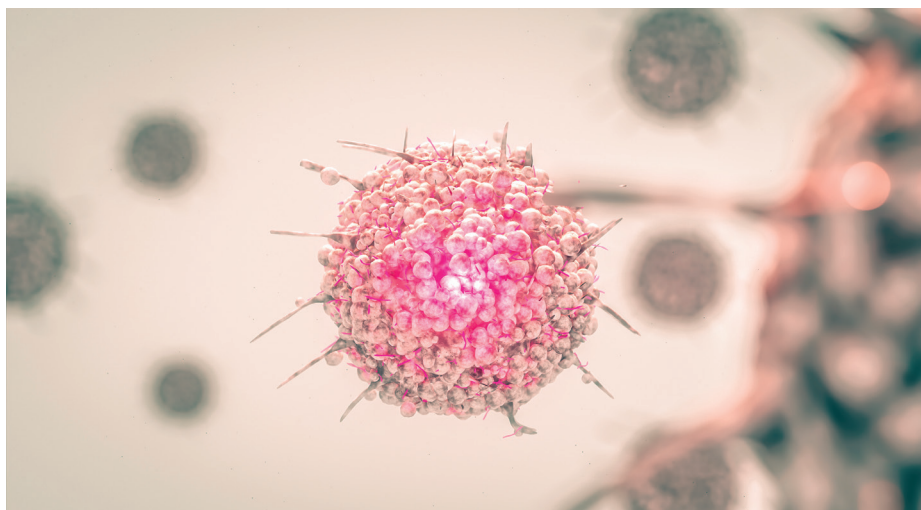
As for the potential key factors behind the relatively higher LOAs in oncology and CNS at the Japanese firms, Said pointed out Takeda, Eisai and Otsuka "tended to have a high number of alliance deals with western countries compared to the rest, specifically Eisai and Takeda."

Those strategic alliances have varied in their form over the past few decades. For instance, Eisai's collaboration with Biogen, Inc. since 2014 for the development and commercialization of Alzheimer's disease drugs has most recently borne fruit in the form of a full US approval for Leqembi (lecanemab).

Leqembi, originally discovered and developed as BAN2401, resulted from another strategic research alliance signed in 2005 between Eisai and Swedish biopharma firm BioArctic AB. (Also see "Leqembi Approval Opens Door To Alzheimer's Market For Lilly And Others" - *Scrip*, 7 Jul, 2023.)

In developing, producing and marketing its oncology product Lenvima (lenvatinib) globally, Eisai also signed a strategic deal with Merck & Co., Inc. in March 2018 to develop both monotherapy and combination therapies with Keytruda (pembrolizumab). The profit share arrangement contributed to widening its global footprint and approvals with Keytruda including for first-line, adult advanced renal cell carcinoma in the US and Europe.

Daiichi Sankyo, meanwhile, began a series of deals with AstraZeneca PLC in March 2019 for the global development and commercialization of antibody-drug conjugates (ADCs), including HER2-targeting Enhertu (trastuzumab deruxtecan). The Japanese firm established a research team focusing on ADCs in 2010 as part of a then strategic pivot to the oncology area. (Also see "Boost For Daiichi's Oncology Ambitions As AZ Agrees Huge \$6.9bn



Deal For Lead ADC Asset" - *Scrip*, 28 Mar, 2019.)

Otsuka's success with its major depressive disorder (MDD) drug Rexulti (brexpiprazole) was predicated on a global collaboration with Denmark's Lundbeck focused on the co-development and marketing of five psychiatric and neuroscience products signed in 2011. The serotonin-dopamine modulator has since been approved in the US and Canada for both MDD and schizophrenia, and in Europe and Japan for schizophrenia.

The Maintena long-acting formulation of Otsuka's own blockbuster atypical antipsychotic for schizophrenia Abilify (aripiprazole) was also co-developed and marketed in collaboration with Lundbeck and Bristol-Myers Squibb, providing another example of the importance to Japanese firms of major global partnerships.

DEALS, DEALS, DEALS

Outside the oncology and CNS areas, Takeda had a high LOA in autoimmune/immunology, reflecting its strategic focus on this field (26.1%) and a prior major acquisition. Before commercializing its now blockbuster inflammatory bowel disease drug Entyvio (vedolizumab) in the US, Takeda has bought originator, US firm Millenium Pharmaceuticals, in 2008.

Likewise, Astellas may not have expected a successful US approval for its non-hormonal menopausal vasomotor symptom therapeutic Veozah (fezolinetant) in May this year had it not acquired for €800m in 2017 Belgian firm Ogeda S.A., which first developed the neurokinin 3 receptor antagonist to the Phase IIa stage.

Astellas's prostate cancer blockbuster Xtandi (enzalutamide) also came to the firm through a global licensing agreement with originator Medivation, Inc., a US company acquired by Pfizer in 2016, which had progressed the drug to Phase II.

OVERSEAS OPPORTUNITIES - ESPECIALLY IN US

Driven mainly by expansion in the US, a research report published by Japan's Office of Pharmaceutical Industry Research in 2021 noted that major Japanese pharma firms' overseas sales ratios grew from 39.3% in 2011 to 59.4% in 2019. It observed that all blockbusters developed by the top nine Japanese companies included the US in their markets.

“

Driven mainly by expansion in the US, a research report published by Japan's Office of Pharmaceutical Industry Research in 2021 noted that major Japanese pharma firms' overseas sales ratios grew from 39.3% in 2011 to 59.4% in 2019.”

Even for relatively smaller Japanese companies, the US remains of central importance. A spokesperson at Kyowa Kirin Co., Ltd. mentioned to *Scrip* recently that the US is the most important market outside Japan, pointing out that 36% of the firm's annual sales in calendar 2022 came from the US, versus 39% from Japan.

**POS: this value is calculated using Citeline's PharmaPremia platform, based on data from Biomedtracker, to see at which points programs either progressed into the next phase or were suspended. A historical analysis of these changes is used to calculate a percentage. For example, if 100 drugs were historically developed for a specific indication but only 40% moved from Phase I to II, that would give a 40% POS from Phase I.*





Lisa Takagi
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Japan

Japan Faces GLP-1 Shortage As Off-Label Diet Use Surges

Grey Areas Between Regulations

Despite repeated warnings by regulatory authorities and physicians' associations, the demand for easy diet aids is impacting the supply of GLP-1 receptor antagonists in Japan.

Japan is facing a supply shortage of GLP-1 receptor antagonists for type 2 diabetes due to their off-label use as diet drugs, prompting the main manufacturers to restrict supplies and calls for their use only in officially approved indications.

Because of the high overall demand, both Novo Nordisk A/S and Eli Lilly and Company have had to limit or even stop providing their respective drugs, Ozempic Subcutaneous Injection SD (semaglutide) and Mounjaro (tirzepatide), which are cleared only for use in diabetes in the country, because of the additional demand.

The companies, along with some pharmacist groups, have highlighted the situation, which the country's public sector including the Ministry of Health, Labour and Welfare (MHLW) has increasingly recognized over the past couple of years. Domestic physicians' associations have also warned of the health risks of off-label use and noted the impact on the supply chain.

Japan's regulations around off-label use are somewhat ambiguous. Although the Pharmaceuticals and Medical Devices Act (PMD Act) bans advertising of unapproved drugs, it does not strictly ban off-label use of approved drugs.

Despite the warnings from both the public and private sectors, the *Pink Sheet* easily found dozens of clinics advertising online for use of GLP-1 drugs for "medical diet" purposes.

SUPPLY RESTRICTIONS ON OZEMPIC, MOUNJARO, TRULICITY

Novo Nordisk announced on 7 August the supply of Ozempic in Japan would be put into limitation or hiatus, suggesting off-label use for weight loss and diet control was behind the move.

"The decision is not due to any malfunctions in the manufacturing process," the local subsidiary of the Danish firm stressed. It requested people "to strictly refrain from using the drug off-label for the purpose of beauty, weight loss and diet," noting that health risks can occur from such use.

KEY TAKEAWAYS

- Lilly's Mounjaro, Trulicity and Ozempic are facing shortages in Japan, requiring restriction or halts on supplies.
- Off-label demand of the GLP-1 receptor antagonists as weight loss drugs is the main reason behind the shortages.
- Despite long-standing warnings from the public and private sectors, online ads and demand for off-label use have persisted, due in part to grey areas in current Japanese regulations.

The subsidiary commented to the *Pink Sheet* that it found the limits to tackling off-label use "frustrating."

Lilly has also limited the supply of Mounjaro since this July, within a month of the local launch of a high dose injection the previous month for type 2 diabetes, because of "increasing demand."

The firm also implored the medical industry "not to use the drug if not for its approved purpose."

For the same reason, the US company has already limited supplies in Japan of another GLP-1 receptor antagonist, Trulicity (dulaglutide), since this March and announced this would continue through August. Upon the decision to continue the restrictions, Lilly again echoed Novo's request to the domestic medical community to halt off-label use for weight control purposes. The request was repeated in a joint statement by Novo and Lilly, AstraZeneca PLC and Sanofi issued in June 2023.

Novo Nordisk Japan explained to the *Pink Sheet* that the August decision to limit Ozempic's supply "was not mainly because of off-label use" but rather because of demand triggered by shortages of its competitors. The firm is in the process of expanding manufacturing capabilities including though new production sites under construction, which necessarily takes time, it noted.

The subsidiary added it recognized demand from off-label use for weight loss in Japan since Ozempic's launch in June 2020, as well as con-



cerns from local physicians' groups. Overall local demand for the drug has surged since the first half of 2021, when the 14-day prescription limit applied to all new drugs was lifted a year following its reimbursement listing under the national health insurance scheme.

"We have taken the off-label issue very seriously," the firm stressed, noting it has been "monitoring off-label use of the products we sold and reporting them to authorities on a regular basis".

REPEATED WARNINGS BY LOCAL PHYSICIANS' GROUPS

Novo Nordisk has limited Ozempic's supply in Japan several times, including February 2022 when one of its manufacturing partners halted its supply under Good Manufacturing Practice inspection.

Other groups have also weighed in on the issue of off-label use. The Japan Diabetes Society first issued a notice asking its members to avoid off-label use in 2020, re-issuing the advise in April 2023, stating use for dieting purposes was "inappropriate" and "not tolerated" by the group.

A 2022 notice from the group noted suspicions behind the stock shortage of GLP-1 receptor antagonists in particular areas, probably due to "mass purchases by beauty clinics for off-label use or inappropriately unequal shipments by wholesalers [to those clinics]," for example in the Shinjuku area of Tokyo, home to dozens of beauty clinics. "If this tendency expands nationwide, it will put diabetic patients at a disadvantage," it warned.

The off-label drugs are usually priced at many multiples of the cost to the patient for approved diabetes use. One beauty clinic, for example, is charging around JPY16,000 (\$110) for one 2mg injection of Ozempic, roughly five times the out-

of-pocket cost for diabetes use under the national insurance scheme.

Japan's largest physicians' group, the Japan Medical Association, has officially condemned physicians who provide the drugs for off-label diet use as "going against physicians' ethics" in separate statements in 2020 and 2022. The group has also asked the MHLW to probe the issue and stabilize supplies.

On 28 July this year, the ministry published another notice asking local health officials to address issues around GLP-1 receptor antagonists, by asking clinics and wholesalers to limit purchases to match needs and avoid stocking up; to use the drugs in an appropriate manner as approved for type 2 diabetes; to prioritize supplies for clinics and pharmacies which actually prescribe the drug for diabetic patients.

The last measure was specifically directed at wholesalers, which it has become clear are willing to supply clinics for off-label use.

OFF-LABEL 'MEDICAL DIET' USE DRIVING DEMAND

While Japan has lower rates of obesity compared with many other developed countries, there is strong demand for diet and weight loss products to meet local standards of beauty and appearance.

A *Pink Sheet* search easily found dozens of online advertisements by beauty clinics, mostly located in Tokyo, offering "Medical Diet" drug products including Ozempic, Novo's Rybelsus (semaglutide) and Victoza (liraglutide) off-label and in some cases Novo's weight control drug Saxenda (liraglutide) - although this has not been approved in the country.

Before and after the launch of Lilly's Mounjaro, several clinics in the Tokyo area were also running

online ads of the drug for weight loss, sometimes referring to its “high efficacy for diet use.”

The clinics often suggest the benefit of the GLP-1 drugs as they “enable weight loss without strict diet control or exercise” and while they may refer to the risk of adverse events, this is often with reassurances that these could be dealt with by visiting the clinic.

There are usually caveats that the drugs cannot be given to people with diabetes (the implication perhaps being that this approved use would be available through the national health scheme) or those with “medical conditions of the thyroid, pancreas and stomach.”

GREY AREAS BETWEEN REGULATIONS

The off-label situation for GLP-1 drugs in Japan reflects grey areas in the regulation of such use and around unapproved drugs.

“Today’s Japanese regulations don’t directly prohibit off-label use of drugs by physicians,” noted Takafumi Mise, a Japanese lawyer at the Higashimachi LPC practice, in a May 2023 blog post on the legal interpretation of off-label use in Japan.

Mise also pointed out the country’s judicial precedents have not imposed strict obligations on physicians to consider the risk of off-label use, although he noted it is possible the country’s Supreme Court would strictly set high standards for physicians’ duty to consider the risks of off-label use if any health damages were caused in patients.

The precedents also tend to regard physicians’ duty to follow the package inserts of pharmaceutical products as very important; such inserts clearly state approved indications, doses and safety warnings, Mise noted.

Although Japan’s PMD Act prohibits both the distribution of personally imported drugs and the advertisement of unapproved drugs, including the product name and efficacy, it does not strictly prohibit online advertisements of therapy with those drugs, nor the use of those by local physicians for “urgent” reasons for “the treatment [of diseases] without any alternative therapeutics in the country.”

In the case of Saxenda (not approved at all in Japan), some beauty clinics are asking patients to self-import and self-inject the drug, which both the MHLW and National Consumer Affairs Center of Japan describe as “very risky acts” for personal health. The center notes it has received reports of adverse effects from the off-label use of GLP-1s, including nausea, headache and dizziness.

PERSONAL IMPORT SITUATION

According to MHLW regulatory research conducted in 2020, Japan is one of the very few developed

countries which allow personal imports of drugs by physicians (as well as by individuals). However, these should be limited to “cases with urgent need for treatment without any alternative therapeutics in the country,” with the medical professionals having to offer the imported drugs to patients in their care or diagnosis under their responsibility.

As for the reason why Japan’s PMD Act doesn’t completely prohibit the personal import of pharmaceutical products, including unapproved drugs, by individuals, the ministry noted the law has been structured so that the country can allow “domestic patients who used to go through therapy overseas to continue this, or to allow international tourists to continue medication during their stay in Japan.”

The research did also note that the use of unapproved or off-label drugs could cause health risks which may not be covered by national Relief System for Adverse Drug Reactions, which provides financial compensation in confirmed cases.

GROWING OBESITY MARKET

While Japan did approve Novo’s Wegovy (semaglutide; the same active ingredient as in Ozempic) in March 2023 specifically for obesity use, it has not been launched yet. The therapy has shown strong growth in the US since its launch in 2021, leading to supply restrictions due to high demand.

While the availability of Wegovy in Japan may have some impact on the use of other GLP-1s in Japan, this might be tempered by its use restrictions. Its use is limited to those with a body mass index of 35 or over, or those with a BMI of 27 or over who also have two out of three of these conditions: type 2 diabetes, dyslipidemia or hypertension.

Beauty clinics sometimes specify a BMI of just 18.5 or over for the off-label use of GLP-1 drugs.

However, recent findings that Wegovy reduced cardiovascular events in obesity patients in the SELECT study may add another layer of value to the use of the drug. (Also see “Wegovy Starting Doses Restrictions Will Continue Through The Year” - *Scrip*, 10 Aug, 2023.) (Also see “SELECT: Novo Nordisk Comes Roaring Back” - *Scrip*, 8 Aug, 2023.)

In the US, several advocates have also been lobbying the Food and Drug Administration to recognize the difference between drugs for obesity and short-term weight loss, noting the importance of treating obesity as a complex chronic disease.

Recently, Lilly recently applied for the approval of Mounjaro in the US for chronic weight management, for which it anticipates an FDA decision by the end of the year. (Also see “Lilly Expects Mounjaro To Benefit From Novo Nordisk Cardiovascular Trial” - *Scrip*, 8 Aug, 2023.)



Jung Won Shin
Senior Editor

Collaborate Rather Than Compete: Korea's Push Toward A Biopharma Powerhouse

Industry Begins To Take Collective Moves

Collaborate. Collaborate. Collaborate. This seems to be the message the South Korean biopharma industry intends to emphasize this year, while the government rushes to unveil measures to support the sector and launches regulatory innovation initiatives.

Korean pharmas are increasingly feeling the need to join hands and work with one another as out-licensing deals, particularly large-scale, cross-border ones, which have been a key part of their strategy over the past few years, fell sharply in 2022.

Meanwhile, Korean bioventures are suffering from funding difficulties amid the generally weak financial and capital markets stemming from global economic uncertainties. According to one ven-

ture capital source, VC investment in the Korean bio/medical sector remains weak, totalling just KRW131bn (\$99.4m) in the first quarter, with series B rounds worth about KRW76.3bn dominating. Only a couple of domestic bioventures, including GI Innovation, launched initial public offerings in the period.

Amid this challenging environment, Korean pharmas, led by the Korea Innovative Medicines Consortium (KIMCo), decided for the first time to co-invest in target companies at home and abroad, marking a step forward for domestic firms which had been making individual moves to find new growth engines and enter global markets.

Such steps have come in line with the government's strategic goal of creating three top 50 global

biopharmas in Korea, two global blockbuster drugs developed by homegrown firms, and doubling biopharma exports by 2027 through a combination of increased R&D investment, stronger support for exports, fostering expertise, as well as regulatory innovation and expansion of the supply infrastructure.

“Korean firms should collaborate rather than compete if they want to go down the global big pharma road,” advised Kevin Kyunghwa Huh, CEO of KIMCo, in a recent interview with *Scrip*. KIMCo was created last year with an aim to serve the collaboration platform for Korean biopharmas.

“

Korean firms should collaborate rather than compete if they want to go down the global big pharma road.”

- Kevin Kyunghwa Huh,
CEO of KIMCo

KIMCO'S CO-INVESTMENT, KDDF'S ADC PROJECTS

After launching a pilot project earlier this year, KIMCo plans to expand into two cycles of investment programs this year. For each selected investment target, it will make joint investments along with a number of Korean pharmas. For the first cycle, investors will mainly comprise Korean firms, while some Korean VCs are also expected to participate.

For the second cycle, KIMCo is inviting participation from global pharma companies, as well as from global VC firms, aside from Korean pharmas and VCs.

In addition, the Korea Drug Development Fund (KDDF) is recruiting domestic companies with antibody-drug conjugate (ADC) technologies, such as antibodies, linkers and cytotoxic payloads, to develop completely homegrown ADC assets. (Also see “The Hunt For Big Fish: How KDDF Is Helping Create Korean Deals” - *Scrip*, 25 Jan, 2023.)

The government agency intends to group these firms together to create a couple of ADC develop-

ment projects and then set up separate companies to progress these. The fund plans to inject R&D financing for each project and also to attract investment from US VC partners, and to seek partnerships with global big pharmas to progress clinical trials and then share profits if development succeeds.

VACCINE DEVELOPMENT FUNDS SEEK STRATEGIC ALLIANCES

Meanwhile, the Korean government-supported vaccine development funds intend to pursue diverse strategic alliances with both domestic and multinational partners. The funds, with an aim to raise KRW500bn this year, are led by Yuanta Investment and Mirae Asset Group. They aim to invest the majority of the total amount in companies conducting clinical trials with new drugs, with a focus on later-stage trials.

Vincent Jeong, managing director and head of venture capital at Yuanta Investment, told a recent webinar that collaborations between domestic pharmas and bioventures and out-licensing assets to global big pharma partners is a good business model, as evidenced by Yuhan Corporation's in-licensing of the oral EGFR inhibitor lazertinib from Oscotec Inc., which was then out-licensed to Janssen Biotech Inc.

However, there haven't been many such successful cases so far in Korea and things will depend on how pharma companies think and their perspectives on investment.

Another challenge Jeong highlighted was that, even if smaller Korean bioventures have convincing data, global big pharma partners may not see such companies as having much credibility. The country's larger domestic players could have a role here to boost the credibility of assets through co-investments or co-development deals with their smaller compatriots.

Meanwhile, Dong-A ST's president and chief scientific officer Jae-Hong Park said in a recent interview with *Scrip* that when Japan's Takeda Pharmaceutical Co. Ltd. began to grow into a truly multinational pharma through acquisitions, it received strong support from the Japanese government, which at the time mediated many activities of the domestic pharma industry. (Also see “Dong-A ST Faces New Wave Of Change As It Challenges Norms” - *Scrip*, 16 Mar, 2023.)

Park believes Korea needs to learn from Japan's example because Korean pharma firms are racing to the US, but doing so only for their own benefit rather than potentially working together in a pre-competitive space and coordinating in certain areas.



Jung Won Shin
Senior Editor

KHIDI Spearheads Support For Korea Biopharma Globalization

Bridge Between Govt, Private Sector



Korea should innovate regulations in line with changing global trends, KHIDI says.

Source: KHIDI

Korea Health Industry Development Institute president Soon-Do Cha talks to *Scrip* how the government agency's support strategy to the domestic biopharma industry may be changing in line with the industry's increased globalization move and how he views the country's policy stance should improve going forward to meet its goal of becoming a strong biohealth nation.

As South Korea seeks to foster the biohealth industry through various strategies including creating new markets, the Korea Health Industry Development Institute (KHIDI) is also making broad efforts in its role as a state-funded agency at the front line of the intersect between the government and private sector.

With the domestic industry's globalization entering a more active phase - the number of Korean biopharma firms advancing into overseas markets tripled to 85 as of 2021, versus 28 in 2015 - the institute is pushing for multiple opportunities for the exchange of technologies. It is also supporting Korean firms' entry into the US and stepping up sup-

port there for potential "K-blockbusters" new drugs.

Although there are still gaps with major countries in terms of investment size and technologies, the Korean industry should steadily increase its own investment, helped by government pump-priming. The government also has a role to play in supporting industry R&D activities to enable leading research in areas with high unmet needs, KHIDI president Soon-Do Cha said in an interview with *Scrip*.

"We need to move toward establishing a basis for qualitative growth through large-scale investment by the private sector and government, as well as strategies to systematically promote the industry to enable the launch of new blockbuster drugs," he declared.

The mission of KHIDI, which operates under the Ministry of Health and Welfare, is to foster the broad health industry in Korea, including in digital healthcare, global competitiveness, regulatory reforms and job creation, while expanding public R&D investment in the field.

KOREAN-TYPE ARPA-H PROJECT

Cha said Korea needs to innovate regulations to keep in line with global trends, including the digital transformation of the industry, diversification of therapeutic modalities and strength in biologics. Regulatory improvements are needed to encourage novel R&D, along with financial rewards for innovation through “premium pricing” for Korea-originated novel therapies, he suggested.

The country also needs to deal with pressing health challenges and to improve review/approval processes and reimbursement systems, particularly for the efficient development and rapid market entry of cutting-edge biologics. “To resolve national issues such as infectious diseases and cancer, as well as to continue to advance the biohealth industry, we need an innovative technology development support model that has strong social impact, despite the high probability of failure,” Cha stressed.

To this end, and taking inspiration from the US National Institutes of Health’s ARPA-H (Advanced Research Project Agency for Health) initiative, Korea is pursuing a similar project by benchmarking key components. These include compensation for high-risk research (supporting highly challenging research with unique approaches and large implications for national health), granting comprehensive rights, including planning, selection and managing, to project managers (who will also have the right to exit projects) and supporting major R&D expenditures (above the project funds currently granted by the health ministry).

“

We need to move toward establishing a basis for qualitative growth through large-scale investment by the private sector and government.”

- Soon-Do Cha, KHIDI President

Adopting a flexible structure to enable networking among various stakeholders that broadly hears views from researchers, patients, the general public and policy-makers is another key factor, the president stressed.

Since the pandemic, digital transformation has also rapidly progressed in the biopharma sector, including precision medicine using genomic and biologic signalling information, as well as drug development using AI and big data to reduce time and cost. New concept digital therapeutics have also emerged.

Against this background, the government and KHIDI aim to create an ecosystem that can deliver customized medicines at appropriate places and ensure continued access to healthcare services.

TAILORED MARKET ENTRY STRATEGIES

By selecting products that will have a competitive edge in particular strategic countries, Korea aims to draw entry strategies appropriate for market characteristics, with the aim of globalizing the domestic biopharma industry, Cha said. Based on size and growth potential, the strategic targets are the US, major European countries, emerging countries in the Middle East and Central/South America, as well as low-income countries.

For leading countries, the intention is to build local bases. For example, KHIDI is already providing opportunities for technology exchange through the Cambridge Innovation Center (CIC) in the Boston biocluster in the US.

Within the CIC, KHIDI has set up an incubation office that is already providing assistance to about 20 Korean firms, including Voronoi, AriBio Co., Ltd., WELT, Yuhan Corporation, Ildong Pharmaceutical Co., Ltd., Dong-A ST and Standigm, which all have offices within the center.

It is also enabling consultations with US experts on setting up companies, progressing clinical trials and regulatory reviews and approvals, as well as out-licensing deals.

The KHIDI-organized Korea Bio Innovation Night and Korea Night receptions in Boston, held during the BIO International Convention earlier this year, drew more than 1,000 biopharma participants, including from multinational pharma firms, reflecting strong interest from potential partners and investors.

For emerging countries, the main aim is to step up provision of information and marketing activities to help Korea’s incrementally-modified new drugs and generics enter such markets.

EUROPE, SE ASIA MARKETS ALSO EYED

KHIDI notes the strategic need to focus on the European and Southeast Asian biopharma markets as well. Europe is worth about KRW300tn (\$22.7bn) and accounts for about 25% of the global biopharma market; it is already a top export market for Korean medicines and home to the subsidiary operations of various firms.

To facilitate entry, KHIDI is providing open innovation opportunities and each year operates the Korea booth at the major Bio Europe meeting. It is also seeking continued cooperation with companies in small but strong European biopharma countries such as Denmark and Switzerland. This November, Novo Nordisk A/S, Roche Holding AG, Sandoz Inc., Sanofi and Merck KGaA, among others, are expected to participate in a partnering event.

Southeast Asia, meanwhile, is emerging as an alternative to the Chinese market in terms of total economic size and population. In particular, Thailand is seen as a country with high potential for Korean firms, given a strong medical tourism sector and well-developed medical infrastructure. Thai firms also focus on low-priced generics, meaning the country depends on imports of key value-added drugs such as anticancers, vaccines and antibiotics.

Moreover, as medicines manufactured in Thailand are exported to nearby ASEAN countries such

as Vietnam, Indonesia and Myanmar, there is large potential for expansion into other regional countries if Korean firms enter Thailand, Cha noted.

INDIVIDUAL COMPANY SUCCESSES

In the case of Europe, which is largely adopting biosimilar-friendly policies, the performances of some Celltrion, Inc. and Samsung BioLogics products are ahead of their reference drugs.

SK Biopharmaceuticals Co., Ltd's anti-epileptic cenobamate has also indicated its potential a blockbuster new drug in the US and its North American presence was boosted by a marketing authorization approval in Canada in June.

In addition, novel Korean drugs such as Hanmi Pharmaceutical Co., Ltd.'s Rolvedon (eflapegrastim), Yuhan Corporation's Leclaza (lazertinib), as well as Korean biosimilar versions of big-sellers AbbVie Inc.'s Humira (adalimumab) and Janssen Pharmaceutical Cos.'s Stelara (ustekinumab), have already received approvals or will do so soon in the US or Europe, KHIDI noted.

In the manufacturing sector, led by large conglomerates Korean firms are building up in the US through acquisition of biologics facilities or setting up their own bases. In line with these moves, KHIDI will closely monitor the US Administration's policy changes stemming from protective trade policies and seek possible measures.





Anju Ghangurde
Executive Editor,
APAC

Big Pharma R&D Chiefs On IRA's Unintended Casualty, Product Life Cycle Compression

R&D heads of Takeda, Amgen, Lilly and Novartis discuss some of the tectonic forces shaping the biopharma sector and the unintended consequences of the IRA on small molecule innovation. Advances in the neurodegenerative diseases segment amid impressive data from donanemab was another key talking point.

If you use the tennis analogy then all-time greats like Novak Djokovic, Rafael Nadal and Roger Federer or the big names on the women's circuit are fierce rivals on court but off the court they celebrate one another's strengths and progress, at least in public.

The recent USA-India Chamber of Commerce (USAIC) Annual Biopharma and Healthcare Summit witnessed similar camaraderie as R&D leaders from Takeda Pharmaceutical Co. Ltd., Amgen, Inc. and Novartis applauded peer Eli Lilly and Company's standout data pertaining to its investigational amyloid plaque targeting Alzheimer's therapy, donanemab. (Also see "Lilly's Donanemab Slows Cognitive Decline; FDA Filing Imminent" - *Scrip*, 3 May, 2023.)

"It's funny because we're in a very competitive industry and in the end we value greatly from each other's successes in many different ways," remarked Andrew Plump, Takeda's president of R&D, at the USAIC session.

"I think it's a great moment for all of us," Plump added.

Even US Food and Drug Administration Commissioner Robert Califf couldn't hold back and cheered the new Alzheimer's results in another session at the summit albeit with a caveat that the data needs to be reviewed before making a judgement. (Also see "For Lilly's Donanemab, US FDA Commissioner Is Already Thinking About Post-Market Questions" - *Pink Sheet*, 3 May, 2023.)

"If the data look as good as the press release this is really exciting," Califf said in what's perhaps a rare public comment on an investigational therapy by the regulator.

On 3 May Lilly reported that the TRAILBLAZER-ALZ 2 Phase 3 study showed donanemab treatment slowed clinical decline by 35% for early Alzheimer's patients compared to placebo, and resulted in 40% less decline on the ability to perform activities of daily living.

Lilly's executive vice president and chief scientific and medical officer, Daniel Skovronsky described the moment though the journey clearly wasn't easy - he had been working in the space for 25 years, with setbacks along the way.

"I had high hopes for this one. The one thing in this business that you learn quickly is you got to stay humble and there's nothing probably more

NEURODEGENERATIVE DISEASE R&D

Big pharma R&D heads deliberated the wider neurodegenerative disease landscape and where things stood on the spectrum.

Amgen's executive vice president, R&D, David Reese noted that industry was now getting proof of principle on clinical trials methodologies, on endpoints and "what actually constitutes a positive result". While that may be a very basic question, it's been one that had been unanswered for many years in the field.

Refining those methodologies, and in particular, developing surrogate markers of effect needs to be one of the clear objectives in the field because "we don't want to go another 20 years or another turn of the wheel as we attempt to do things empirically and we can't do it trial-by-trial because it simply takes too long," he explained.

"Understanding intermediates and surrogate predictors of efficacy and safety is an area where the field needs to shine a bright light right now," Reese added.

Lilly's executive vice president and chief scientific and medical officer, Daniel Skovronsky, kept the tenor upbeat, suggesting that Lilly was not done yet; the next step is to "go even earlier" and the company was doing prevention studies, which probably holds even greater promise for amyloid modulator drugs, while also working on tau targeted drugs for Alzheimer's disease, he indicated.

"Alzheimer's is one of many neurodegenerative diseases, and maybe progress on Alzheimer's empowers us to think more boldly about other neurodegenerative diseases and maybe we can have similar progress on some of these others. The technologies are there today -we're starting to see progress on dreaded things like ALS [amyotrophic lateral sclerosis], more to come on Parkinson's, and frontotemporal dementia," he added.

Fiona Marshall, President, Novartis Institutes for BioMedical Research, noted the over the last 10 years there has been a much better fundamental understanding of some of the neurodegenerative diseases from a mechanistic point of view, greatly informed by human genetics.

But the challenge has been that "we know what the targets are, but how do we actually drug these pathways?" the former MSD executive said, also referring to the difficulty with getting molecules into the brain, particularly large molecules. Marshall was previously senior vice president and global head of discovery sciences, preclinical development and translational medicine at MSD, as Merck & Co is known outside Canada and the US.

"I'm hopeful that advances in better delivery, for example, into the CNS will allow us to bring other modalities on the same targets. From our point of view, we're concentrating a lot on oligonucleotide therapies and siRNA delivery mechanisms into the CNS," Marshall said.

Novartis is also working on neurodevelopmental and rare CNS disorders using gene therapy and efforts are underway to address some of the challenges.

"It will be fantastic if we rather than having to give patients repeated infusions, or whatever it is, if we can really help patients with treatments that are not a burden to them, but also show the real benefit of hitting these pathways. That's what we've got to ultimately aim for," she added.

Takeda's president of R&D Andrew Plump similarly referred to the triad of targets, modalities and biomarkers to move things ahead.

Nevertheless, the industry veteran indicated that the challenges are still immense in neuroscience given that lot of the diseases don't have clear genetic predispositions and putting a drug into the CNS has its uncertainties since "there's a lot that we just don't understand about the brain". Besides, these trials can be "quite difficult".

Plump, who has held leadership positions in Sanofi and Merck & Co., Inc. along the way in his three-decade long career across pharma and academia, notably also stated that the policy landscape and agencies are not as "forward-thinking in CNS diseases as they need to be" given the large unmet medical need.

humbling than data readouts in Alzheimer's disease. So, I ran into it being ready for anything and this readout met my most positive hopes for what could be achieved in this disease," said Skovronsky.

He was ecstatic for patients, but also for his team of scientists and drug developers, having watched all of them "put their lives into these drugs".

"So, a lot of tears of joy for people who've worked really hard," Skovronsky said in response to a query from moderator and co-founder of Rallybio., Martin Mackay.

On the bit around competition, Skovronsky

said that was a "good thing", often just "inspiring" each other to try and make better products, which benefit patients.

"I think it's a terrific example - the Lilly-Novo Nordisk competition in diabetes and obesity - it has just led to better and better drugs and more understanding of science, beneficial conditions," he added when Mackay referred to firms rubbing against each other at times on the same program.

The high-profile panel also touched upon where things were headed in the neurodegenerative disease R&D segment.

IRA AND SMALL MOLECULE DEVELOPMENT

The session on R&D Strategies and Trends, which traditionally marks the closing panel discussion at the USAIC event, also saw the industry heavyweights weigh in on the burning topic of the Inflation Reduction Act (IRA) and its “unintended consequences” when it comes to areas like small molecules.

Amgen’s executive vice president, R&D, David Reese referred to certain key tectonic forces including price deflation that were set to shape the biopharma industry over the next few decades, including tailwinds and certain headwinds.

Reese noted that pressures on healthcare budgets around the world aren’t going away and had been exacerbated by the pandemic and could take years to play out; in the US it had been brought “front and center” by the IRA.

“That’s just part of the mix as we think about how we invest in a portfolio - what’s the therapeutic area mix/the modality mix? How are you going to stage investments?” the Amgen long-timer who joined the company in 2005 pointed out.

Areas of concern, the Amgen executive said, included small molecule oncology development, where there perhaps “won’t be time to do the stepwise sort of development” from late lines of therapy to the adjuvant setting. “So you have to think about those development programs in a different way. In the end innovation will succeed but how you invest along the way, it will definitely change because of this phenomenon of price deflation,” Reese said.

LIFE CYCLE COMPRESSION

Among the other tectonic forces, the tailwind is demographic change. With societies aging globally, pharma will need to be an important part of the solution to deal with a host of problems; neurodegenerative disease may be front and center in terms of challenges societies will face, Reese predicted.

The other tailwind is simply being in an era of just “unbelievable technology” that’s changing rapidly. Pharma, he noted, is facing forces such as life cycle compression. (Also see “Amgen, J&J, Takeda R&D Heads On The Era Of Human Data, Treating Disease Earlier” - *Scrip*, 4 Jul, 2022.)

While in the past a drug’s lifecycle was typically defined by patent expiry, going forward, more often than not, the lifecycle will likely be defined by when it becomes ‘technically obsolescent’, which may predate loss of exclusivity by some years.

“So you just have to think about that when you’re thinking about how you make major investments,” Reese cautioned.

‘DOESN’T MAKE SENSE TO DISCRIMINATE AGAINST SMALL MOLECULES’

Lilly’s Skovronsky was direct, noting the “arbitrary distinctions” pertaining to small molecule medicines, which includes “strangely” small interfering RNA (siRNAs) among other drugs, and come under price negotiation after nine years, whereas large molecule biologics are protected for 13 years.

“Nine years just isn’t enough for any kind of molecule; it doesn’t make any sense to discriminate against small molecules, particularly in chemistry projects. If anybody thought about this, no one would think it is easier to make a small molecule drug than an antibody; small molecule drugs are some of the hardest things we do,” Skovronsky asserted.

If anything, small molecules perhaps require extra protection, he added.

The IRA enables Medicare to negotiate drug prices for small molecule drugs nine years after they reach the market starting in 2026 and for biologic drugs 13 years after they reach the market commencing 2029. Industry experts believe that such uncalled for distinction could see companies defocus small molecule programs.

The Lilly executive further noted that small molecules are convenient for patients, they are usually oral and quickly genericized, “so when the patent goes off, they’re readily copied - essentially free for society”.

“So it’s strange that Congress put a disincentive for small molecule innovation,” he stated.

Skovronsky further added that nine years isn’t enough time to do some projects, “not enough time to do new indications or really maximize opportunities”. Pharma’s go-to-strategy in the past in general has been what indication can it do the fastest - it’s usually something small - and then “get the drug out there and start learning and getting used and then expanding indications”.



“So depriving patients who belong to smaller categories of disease - just a lot of unintended consequences here with the nine years. If we could get that changed to 13, that is something we can work with. Otherwise, I see it as a huge detriment to a pretty significant chunk of research.”

Lilly’s own portfolio includes products like Verzenio (abemaciclib) which was approved by the US FDA in 2021. At the time the small molecule CDK4/6 inhibitor was the first addition to adjuvant endocrine therapy approved by the agency in nearly two decades for the treatment of HR+ HER2- early breast cancer.

The Lilly executive has over the recent past come out sharply against how the IRA provision, if it were enacted at the time, would have perhaps served as a disincentive to pursue investments in such vital therapies.

Fiona Marshall, president, Novartis Institutes for BioMedical Research similarly referred to certain negative consequences around IRA’s drug price-setting provisions.

Pharma, she maintained, would want to choose the best modality from the point of view of the patient rather than getting “something more complicated” because of policy disincentives.

“So many times the first indication, it’s just the entry point and then you’re actually going into other indications, or you have new delivery schedules, new dosing schedules, and it just becomes more difficult to bring that added value. So that’s a real concern,” Marshall stated.

Complex modalities like siRNA therapies are part of small molecules at the moment, she added.

Novartis CEO Vas Narasimhan had earlier this year at another industry summit highlighted the revolutionary potential of technology platforms such as siRNA; what makes these treatments “so powerful”, is that rather than using oral drugs

daily, you can take medicines every six months and “see dramatic reductions in things like cholesterol, maybe in the future for blood pressure or other metrics of cardiovascular disease,” the CEO said at the time. (Also see “BioAsia 2023: Leaders from Novartis, Apple Talk Innovation, Tech, Data Privacy” - *Scrip*, 28 Feb, 2023.)

The US Food and Drug Administration (FDA) had in 2021 approved Novartis’s Leqvio (inclisiran), the first and only siRNA therapy at the time to lower low-density lipoprotein cholesterol (also known as bad cholesterol or LDL-C) with two doses a year, after an initial dose and one at three months.

IRA ‘NOT ALL BAD’

Back at the USAIC summit, Takeda’s Plump, who has long emceed the event with panache, had a distinct view around the impact of the IRA, suggesting that there are elements of the legislation that are “quite positive” for patients and for access to medicine and so “it’s not all bad”, though there is an inherent threat in the IRA to innovation that industry needs to get its head around.

While Takeda for one is strategically focused on diseases that may not be “influenced too much by the IRA” and hasn’t made any pipeline prioritization decisions or decisions around indications that are driven by IRA, “it does affect strategically how we think about sequencing indications, how we think about resourcing parallel versus sequential activity”.

“We shouldn’t actually be using the IRA as a crutch for making decisions. I’ve seen some companies do and I don’t like it. But overall, on balance, I think we can watch where it goes. I think it’s not terrible, but it will have ramifications,” Plump declared.

The Pharmaceutical Research and Manufacturers of America (PhRMA) had earlier indicated that the IRA’s drug price-setting provisions were already having an impact on biopharmaceutical R&D decisions, with several manufacturers announcing cancellations of pipeline projects as a direct result of the law. (Also see “IRA Effect: Alnylam Acting ‘Rationally’ In Halting Second Orphan Indication For Amvuttra - Analysts” - *Pink Sheet*, 7 Nov, 2022.)

A 2022 survey of PhRMA member company leaders suggested that a majority had concerns; three-quarters of the leaders surveyed said the IRA creates significant uncertainties for R&D planning and that they already are reconsidering R&D investment strategies, while 78 percent reported that early-stage pipeline projects are likely to be cancelled due to IRA provisions. Importantly 63 percent of respondents indicated that they expect to shift R&D investment away from small molecule medicines, the industry body said.





Brian Yang
Managing Editor

Storm Coming? Commercial Compliance Crackdown Shocks China Pharma Industry

Toughest Moves Yet

In a new wave of crackdowns on compliance in the pharma sector in China, 10 medical meetings have been cancelled in short order, while sector-wide stock prices have plunged and 100 hospital officials placed under investigation, shocking the industry.

In China's latest crackdown on irregular practices in the pharma sector, not only company-organized meetings but physicians' conferences run by professional medical associations are being cancelled one after another.

While major cities such as Hangzhou and Chengdu cited "security concerns" due to international sports events as among the official reasons, others have simply scrapped all such gatherings.

Amid a tough new wave of official actions, the reactions from the industry have been swift. Firstly, many domestic drug makers announced a halt to academic promotion meetings or scrapped plans

for other get-togethers, while some multinationals are re-organizing their medical rep force and commercial business units, with some even started to let employees go.

KEY TAKEAWAYS

- "Cash-for-sales" is the major focus of China's new pharma commercial compliance crackdown.
- Many medical rep visits and academic meetings are being scaled back or cancelled for the time being.
- Many expect the crackdown to last over the remainder of this year and even into next.

Hospitals are also not being spared, as more than 100 officials and Communist Party General Secretaries have been placed under official investigation since July.

On 28 July, a joint conference organized by the National Health Commission and nine other state agencies announced a one-year crackdown campaign on corruption in the pharma sector. On the same date, the Central Disciplinary Committee under the Chinese Communist Party (CCP) held a video conference announcing it will work to weed out the types of corruption seen as prevalent in the industry.

The official announcement on the committee's website calls for sector-wide action, covering the full value chain and promising a systematic overhaul. The focus is on officials and their cadres and staff working in key positions.

Both those offering and receiving bribes will be subject to prosecution and punishment, the announcement warns.

NEW FOCUS ON PHARMA

In effect, the document about the crackdown was issued by May, but got little attention until the influential Central Disciplinary Committee wielded its power and joined the campaign.

Under Chinese President Xi Jinping, who has put corruption and common prosperity at the center of his policies, the Chinese government has initiated rounds of clampdowns on tech giants and online tutor service providers - but so far the pharma sector has received little attention.

This now seems to be changing as the health sector, along with education, are seen as two key areas directly impacting the livelihood of the Chinese people.

The document issued in May gave an outline of the target areas for the crackdown within pharma, one being drug procurement processes.

"The emphasis is on cash-for sales during drug sales, engaged in by drug manufacturers, sellers and medical representatives," notes the document.

VBP IRREGULARITIES

China's volume-based procurement (VBP) scheme is laden with irregularities, including that some hospitals refuse to follow through with bid-winning contracts and instead set up obstacles to deter the winning products from entering hospitals. Instead, they procure other higher-priced drugs due to "cash-for-sales" kickback practices (known as "Daijinxiaoshao" in Chinese).

“

The emphasis is on cash-for-sale practices during drug sales, engaged in by drug manufacturers, sellers and medical representatives.”

- China Central Disciplinary Committee

The VBP scheme has attracted much attention due to the high volumes at stake. To slash the prices of off-patent drugs, the Chinese government first implemented VBP in 2018, initially in 11 pilot cities, and then quickly expanded the program to public hospitals nationwide.

The high product volumes and sales values for inclusion of a single drug was seen by authorities as justifying the often very aggressive cutting of prices.

However, VBP has also provided some hospitals with opportunities to evade the scheme and instead to procure from certain manufacturers that offer cash incentives, a practice that is now becoming the epicenter of the crackdown.

SPENDING RED FLAGS

One red flag that pharma firms could be subject to the new clampdowns is usually high promotion expenses.

One company cited by the CCP's disciplinary watchdog is publicly traded Yipinhong Pharmaceutical Co., Ltd., which specializes in pediatric and





vaccine products. Within its total sales expenses of CNY1.25bn (\$174m), “academic and market promotion expenses” accounted for the vast majority at CNY1.19bn. In comparison, R&D spending was CNY190m (including direct expenses of only CNY55m (4.3%)).

The high ratio of 21.5 times sales, marketing promotion versus R&D spending has raised eyebrows among investors, who have questioned whether the firm is mostly focusing on selling or developing new products.

Promotional activities are typically carried out via academic conferences organized by pharma companies and hosted by national or provincial medical and physicians’ associations.

Unlike previous rounds, the latest clampdown appears to be targeting physicians and medical associations, pointing to drug makers “using academic activities, hosting or attending medical conference as a pretext to accept donations.”

With many such conferences being cancelled, it signals the new crackdown is thorough and coordinated. Since July, a total of 155 hospital chiefs or CCP General Secretaries have been placed under investigation, the Daily Economic News reported.

SHARE PRICES AFFECTED

Meanwhile, Chinese provincial disciplinary authorities, such as in populous Shandong province, have also hosted video calls to highlight the crackdown activity.

This is already affecting share prices. At market open on 7 August, nearly all publicly-traded pharma stocks on the Shanghai and Shenzhen markets were dropping. As well as Yipinhong, Livzon Mabpharm Inc’s parent Livzon Pharma and Changchun HT Bio have so far been hard hit and

even major player Jiangsu Hengrui Medicine Co., Ltd. was not spared.

One of the worst affected is Shanghai Serum Biotechnology Co LTD, a specialty producer of snake bite serum treatments. On 31 July, the company announced its president Fan Zhihe had been detained for further investigation and that Fan’s son had taken the reigns of the company. Its stock had nosedived over 13% in two days.

REPS, RECORDS

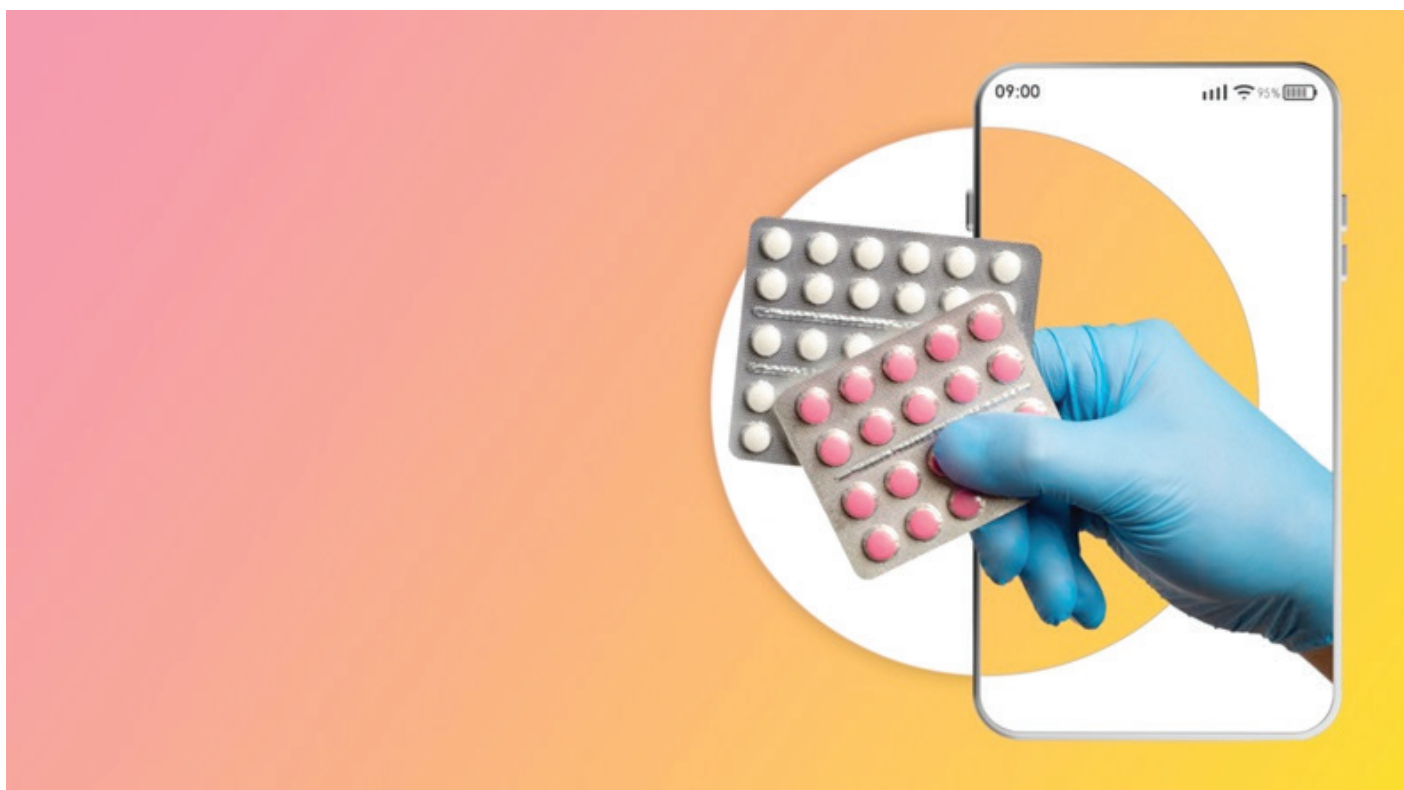
Some multinationals are also finding themselves in hot water. Some have scaled back rep visits to hospitals, while Novartis AG even received an unprecedented request from a major Shanghai hospital.

Changzheng Hospital, or China Navy Medical School Second Affiliated Hospital, sent an official notice to the Swiss giant requesting the reprimand of four reps, citing measures taken as a response to disciplinary inspections. In a response, Novartis China said that the company has received one request from the hospital. Out of two sales reps involved, one has left the company in 2018 and another has not been hired.

Novartis continues to hold high standards and will continue to investigate the matter, noted the company.

Meanwhile, there have been other reports sending shock waves through the already fragile sector. Authorities are said to have taken away storage devices holding years’ worth of transaction records, as well as health information system files.

The rumored company, Hengrui, has denied any such activity, but many firms are now worried that the next focus in the clampdown will be sales transaction records.



Anju Ghangurde
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Heat On E-Pharmacies In India - The Shape Of Things To Come

India is expected to rein in the 'unfettered' run of e-pharmacies, a segment where top Indian conglomerates and Amazon have made strides, with pharma intertwined having tapped into these platforms. *Scrip* speaks to experts on areas of concern including prescription 'workarounds', supply chain transparency and data privacy where more oversight is called for amid the evolving regulatory landscape.

E-pharmacies find themselves in a delicate situation in India, after what experts termed as a generally 'unfettered' run.

They are facing the heat for allegedly violating India's drugs regulations while on the flipside specific draft rules pertaining to the sector haven't been actioned for which a Parliamentary Committee has nudged the health ministry to get moving, fast.

Things came to the fore recently after close to two dozen e-pharmacies including big names such as Tata1mg, Netmeds and PharmEasy, were reported to have received show-cause notices for

allegedly violating the provisions of India's Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetics Rules, 1945.

It's not immediately clear if Amazon, which was among the e-tailers named, did indeed end up receiving the notice as well.

The notices came against the backdrop of continued strong opposition from the brick-and-mortar pharmacy body, the All India Organization of Chemists and Druggists (AIOCD), among others like the Pharmacy Council of India. Things were accentuated amid reports in the media that the health ministry may go as far as barring e-pharmacies, though most pharma industry pundits believe that such an extreme step is less likely.

There's quite a bit at stake in the Indian e-pharmacy space. It's a sector that in the past saw significant private equity interest with firms like Sequoia, Temasek and Eight Roads, among those making investments though there has been early consolidation in the segment. It now has some

large Indian and foreign players including the Tata group, Reliance Industries Ltd (RIL) and Amazon vested in the space.

Tata Digital acquired a majority stake in 1mg in 2021, while 2020 saw India's largest private sector corporation RIL seal a deal via its subsidiary Reliance Retail Ventures Limited to acquire the online pharmacy Netmeds. Amazon Pharmacy was launched in Bangalore in 2020. (Also see "Amazon Pharmacy Starting Up In India: What Pharma Could Gain Or Lose" - *Scrip*, 18 Aug, 2020.)

What's more is that pharma has over the recent past tapped into these platforms – for instance Pfizer's Patient Access Programs (PAP) India, a mobile application designed to ease and fast track enrolment to the US multinational's PAP, is executed by Tata 1mg.

"We are looking at pulling in a host of value-added services in the convenience of a mobile app, which will improve patient experience as well as cost of care," Pfizer India's then country president, S Sridhar, said at the time of launching the app last December.

In February this year, Tata 1mg, launched a comprehensive online cancer care platform that hopes to emerge as a one-stop destination for those with cancer and their families to access reliable and accurate information.

STRINGENT OVERSIGHT, NOT BAN?

Industry pundits tracking the high decibel activity in the e-pharmacy space asserted that an outright ban isn't a solution; they also believe that the gov-

ernment and the regulator are "smart enough" to see the value that the e-pharmacy model offers to people and not react to the "unwarranted alarm" raised by the incumbents.

"That said, an emerging area is quite fluid because regulations always trail innovation and the lag time offers a chance for some fringe elements to take advantage of the space. Therefore, more stringent oversight will be required," Salil Kallianpur, a former executive vice-president at GSK in India, told *Scrip*.

Kallianpur noted that the success of the e-pharmacy model depends on convenience and trust – over-regulation could erode those qualities and hence, a balance is required to maintain oversight to ensure increased consumer benefit while protecting the market for genuine players.

An investment banker tracking developments suggested that tighter regulations pertaining to e-pharmacies, factoring in some "wins" for traditional pharmacies, which should placate them, appear to be the way forward.

"An outright ban on e-pharmacies per se looks out of the question," he told *Scrip*.

Others like industry veteran and president and CEO of Danssen Consulting, Dr Ajit Dangi, underscored that digitization of commerce is here to stay and it wouldn't be prudent to ban online pharmacies. He, however, maintained that claims by e-pharmacies that they are complying with the Information Technology Act "do not hold water" as they are selling prescription medicines to the patients which must be regulated under the Drugs Act.

NOTIFY RULES, SAYS PARLIAMENTARY PANEL

In late March, an Indian Parliamentary panel, following up on its report last year, highlighted that online sale of medicines in India had not been regulated "despite objections and concerns" raised by stakeholders.

It noted that no decisions had been taken on the recommendations made by Group of Ministers (GoM) and opined that the delay in such crucial policy matter is "not conducive to the fast-paced digital market". The Prime Minister's office had in 2019 constituted a GoM to further examine the details of the proposal to notify E-pharmacy rules and make suitable recommendations.

In 2018, India notified draft rules pertaining to the sale of drugs by e-pharmacies, including specifics around plans for "transaction audits" and periodic inspections of such pharmacies. (Also see "India Builds In Transaction Audits For Monitoring E-Pharmacies" - *Pink Sheet*, 5 Sep, 2018.) (Also see "India's E-Pharmacy Rules – Balanced And A Leap Of Faith On Patient Data Security?" - *Pink Sheet*, 1 May, 2018.) Offline chemists and druggists associations had opposed these arguing that approximately 800,000 chemists would be "out-priced" and go out of business. Among a string of other concerns, they also flagged up the potential of misuse of data available online with e-pharmacies.

The department related standing committee on commerce, in its reported presented to the Rajya Sabha on 24 March this year, has urged India's ministry of health and family welfare to notify e-pharmacy rules and formulate comprehensive guidelines with regard to e-pharmacy/e-health platforms.

Last year, the Committee said that it was "appalled" that the draft E-Pharmacy Rules had not been finalized. While it appreciated the rise of e-commerce in the pharmacy and health sector, the panel expressed concern at the possible misuse of such avenues for distribution of "illegal or unethical medicines or outdated, substituted, or counterfeit medications amid the absence of regulations".



“What we really need is amendment of the Drugs Act with clear and concise guidelines to regulate this trade effectively, so that fly-by-night operators are weeded out and the supply chain remains free from spurious drugs,” Dangi, a former president and executive director of Johnson & Johnson in India, told *Scrip*.

An estimated 50-plus e-pharmacies are said to be operating in India, as per a 2020 report by the Federation of Indian Chambers of Commerce & Industry; they saw significant traction during the pandemic-related lockdown - 9m households used e-pharmacies in May 2020 versus 3.5m in fiscal year 2020, the report noted.

Some online pharmacies had earlier specified that their digital platforms come under the purview of India’s Information Technology (IT) Act 2000, though they have alongside sought clarity on norms/guidelines to allow legitimate participants to grow.

“The model followed by Indian Internet Pharmacy Association (IIPA) members is fully compliant with the law. We have a digital platform governed by the IT Act, which transmits the prescription to an existing offline licensed pharmacy,” IIPA president Prashant Tandon was reported as saying by the *Press Trust of India*. Tandon is also cofounder and CEO of Tata 1 MG.

The IIPA is demanding a level field for all players in the e-pharmacy space, “without favor or bias”.

Sources in the e-pharmacy segment suggest that the government is more widely concerned about counterfeit drugs entering the supply chain and essentially has the interest of patients in mind.

“The answer lies in regulation, rather than a ban,” an executive told *Scrip*, also pointing out that traceability is generally higher in online sales.

Last year, India had proposed a draft New Drugs, Medical Devices and Cosmetics Bill, 2022 as it seeks to “keep pace with changing needs, times, technology”. The draft included a provision that empowers

the central government to make rules to “regulate and restrict for online mode of sale, or stock or exhibit or offer for sale, or sell or distribute”, of drugs; internal consultations on a revised draft of the 2022 bill are believed to be ongoing, but the specifics could not immediately be verified.

PRESCRIPTION SHORTCUTS

The value and role of e-pharmacies in delivering medicines and services to patients notwithstanding, experts point to some key areas of concern, especially “workarounds on prescriptions,” as one expert put it.

An industry expert told *Scrip* that there ought to be greater scrutiny on the supply chain when it comes to e-pharmacies to ensure spurious drugs don’t enter the system, while their “predatory pricing approach” isn’t sustainable for the wider ecosystem.

“Data on purchases, the supply chain should be available and reviewed – we need greater safeguards in these areas,” the industry veteran with a multinational firm explained.

Ex-GSK executive Kallianpur said that while e-pharmacies adopt an e-commerce model of online ordering and supply, the basics of ensuring that Rx medicines are dispensed against “valid Rxs of doctors” should not be compromised upon.

“There have been certain instances where this process has been ‘simplified’ by ensuring that they have doctors of their own calling consumers, ‘examining them’ over phone calls and issuing prescriptions of the medicines they want to buy. These kinds of shortcuts, while preserving customer relationships and ensuring sales, can cause long-term damage if human lives are lost,” Kallianpur asserted.

BULK PURCHASES – COST OVER-RIDING QUALITY?

Procurement and quality aspects are also prickly issues when it comes to online sales of medicines. A key factor of the scale that online pharmacies have enabled them to purchase in bulk from manufacturers directly, and sell directly to customers, Kallianpur noted.

“By avoiding the entire distribution chain, they save 30-45% (wholesaler + retailer margins and cost efficiency on bulk purchases) which they pass onto customers. This is probably the real reason for AIOCD’s concern as it directly impacts the business of wholesalers by bypassing them,” explained the executive, who now runs a digital health consultancy.

While this augurs well for customers, there is limited oversight on the quality of the medicines that are purchased; such bulk purchases could

mean that “cost overrides quality in priority,” he maintained.

“At this point of time, e-pharmacies are buying quite a bit from listed pharma companies. However, as they scale up, look for more cost efficiency and build white-label/private label businesses, the threat of inferior quality purchases can go up. Putting stringent systems in place is a must to avoid any untoward incidences,” Kallianpur asserted.

Danssen’s Dangi similarly re-emphasized that e-pharmacies have advantages as medicines are home delivered and the patient can save up to 20-30 percent in cost with middlemen being eliminated - this again has a direct business impact on brick-and-mortar pharmacies.

On the flip side, though, Dangi said that most retail chemists sell ‘scheduled drugs’ without prescriptions and many of them do not have registered pharmacists on the premises as required by the law. Under Indian drug regulations, Schedule H, H1 and X include certain prescription medicines that can be sold only on the prescription of a registered medical practitioner and narcotic and psychotropic substances-based drugs.

“Antimicrobial resistance has reached epidemic proportion because of misuse of antibiotics as they are available without prescription and often home delivered merely on a phone call without prescription. This has to stop forthwith,” the industry veteran asserted.

DATA PRIVACY, MOVING BEYOND JUST ONLINE DRUG DISTRIBUTION

Data privacy is another grey area, with the investment banker quoted previously suggesting that strict norms in the area and on substitution could make life tougher for e-pharmacies and even dull the sector’s shine.

Ex-GSK executive Kallianpur noted that e-pharmacies collect a lot of private medical information of their customers and like any digital-first company such data is “invaluable” to them.

“Having robust cybersecurity systems in place to avoid hacks and loss of data will be very important. Ensuring data privacy and not selling data to advertisers etc. will be another priority,” he added. (Also see “Ransomware Attacks: The State Of Play As Indian Firms Mount Defense” - *Scrip*, 30 Mar, 2023.)

Some internet-based platforms that facilitate the sale of medicines and view themselves as intermediaries believe they are protected as such via section 79 of India’s IT Act from any liability, for any third-party information or data made available by them, though such cover is conditional.

Meanwhile, amid the evolving regulatory maze, experts also believe that the pure online distribution model of e-pharmacies don’t hold great

prospects in the long term.

“I don’t anticipate any major fresh PE transactions in the pure play e-pharmacy space; most players sold to the larger groups (except perhaps in the case of one large e-pharmacy) and in any case the margin profile never really stacked up, so it wasn’t too easy for financial investors to keep funding the space,” the investment banker explained. (Also see “2021 Deal Action In India: Watch Private Equity And E-Pharmacy” - *Scrip*, 4 Jan, 2021.) (Also see “Six Global Trends That Could Lift Or Drift India Pharma In 2021” - *Scrip*, 5 Jan, 2021.)

“The way e-commerce grew over the recent past, we haven’t seen the same growth for pure play e-pharmacies. It’s not a business that has really scaled across the board on the technology front as was anticipated some years ago”.

Kallianpur said that if e-pharmacies develop into merely drug distributors, then the model will be unsustainable and offline pharmacies will eventually do better because of “sheer presence, customer trust and a hyperlocal presence”.

The real opportunity for these online companies, he believes, is to develop into strong engagement platforms for health consumers and not just the sick.

“There is a rapidly evolving awareness on ‘staying well’ and taking care of your own health amongst the young. Health platforms can offer a slew of services in wellness, nutrition, skin/haircare, supplements, exercise and diet.

“Some platforms have begun to do this and make money from information, counselling, selling insurance and diagnostic tests, helping with doctor discovery etc, and treat medicine distribution as a commodity,” he noted.

When these companies evolve into platforms and understand the power of digital-first services that help them serve at scale, then they will realize their true potential, he added.





Anju Ghangurde
Executive Editor,
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McKinsey Exec On Generative AI in R&D And Pharmacovigilance, Digital Twins

McKinsey & Company's senior partner Vikas Bhadoria, in this first instalment of a wide-ranging two-part interview with *Scrip*, outlines a number of use cases to define where pharma currently is and the potential value that can be unlocked as industry adopts new technologies such as generative AI, digital twins and the metaverse.

New technologies like generative artificial intelligence (Gen AI) and digital-twins could potentially rewrite the life sciences sector, with several promising use cases across the molecule-to-market continuum.

The excitement, laced with some trepidation, over Gen AI across businesses and society at large has been quite extraordinary. Poster child OpenAI's chatbot, ChatGPT, drew one million users in just five days post launch - in comparison Netflix took an estimated three-plus years to garner a similar user base. (Also see "ChatGPT Unleashed: Generative AI Use Cases Taking Off In Pharma" - *Scrip*, 6 Jun, 2023.) (Also see "The ChatGPT Revolution Comes To Pharma Business, Starting With Medical Congresses" - *Scrip*, 22 Mar, 2023.)

Business executives too have taken to these

new technologies, with recent studies suggesting significant use, across sectors, of Gen AI tools by the C-Suite for work. (Also see "This Is The Way Of The Future: Digital Health Experts Share Thoughts, Experiences With Generative AI" - *Medtech Insight*, 18 May, 2023.)

More widely, Gen AI is expected to deliver substantial productivity improvement across business functions and also alter the workforce.

In this first part of a wide-ranging interview with *Scrip*, Vikas Bhadoria, senior partner, McKinsey & Company, outlined use cases in areas such as target identification where the global management consultancy could help a pharma client deploy a "clinomics" approach to establish a proof-of-concept genomics platform for a single therapeutic area in under eight weeks.

Gen AI can also be effectively deployed for "customized communications, scripts and content," noted the McKinsey long-timer, who has worked in multiple countries/regions including India, China, Japan, Russia, the UK, North America and the Middle East.

R&D is where Gen AI's high-impact value gains potentially lie. It's also an area that's seen big picture action - for instance earlier this year, Mitsui & Co., Ltd. and AI chip giant NVIDIA teamed up for Japan's first Gen AI supercomputer for the pharma industry. Leading pharma companies and start-ups in Japan, reports said at the time, are expected to use the collaboration's Tokyo-1 NVIDIA DGX supercomputer to accelerate drug discovery.

McKinsey expects generative AI to have a significant impact on the pharmaceutical and medical-product industries - from \$60bn to \$110bn annually - it said in a recent report. The huge potential reflects the resource-intensive process of discovering new drug compounds; pharma companies typically plough in about 20% of revenues in R&D, with new drug development taking an average of 10-15 years.

Gen AI is expected to unlock significant value, improving both the speed and quality of drug discovery. Bhadoria, though, underscored the need



Vikas Bhadoria, senior partner, McKinsey & Company.
Source: Vikas Bhadoria



for more detailed quality checks on AI-assisted processes going forward in the wide-ranging interview, which will also cover other areas such as drug shortages and quality compliance in its next instalment.

The executive, who leads the global management consultancy's Life Sciences Practice for India and the Pharmaceutical and Medical Products (PMP) Operations Practice in Asia, also touched upon the growing adoption of the "digital twin" technology across various functions in the pharma value chain including the first examples in planning and scheduling. (Also see "Re-Configuring Pharma Operations Amid Pandemic Strains" - *In Vivo*, 8 Apr, 2021.) (Also see "McKinsey Exec On Technology Trends Reshaping Future Factories" - *Scrip*, 9 Mar, 2022.)

"The models mimic all the constraints that exist, such as demand, lead times, and equipment capacities, but also shelf life, different market authorizations, number of people on shift on a given day, and batch sizes," explained Bhadoria.

Digital twins are already being deployed by some pharma firms as part of their smart manufacturing efforts. For instance, in 2021 GSK plc announced a successful proof-of-concept of a digital twin approach for vaccine manufacturing with Siemens and Atos, which uses machine learning and modelling to provide new insights for optimizing the development and manufacturing of vaccines. (Also see "GSK CTO, Boehringer Exec On The Metaverse And Pharma's Foot In The Door" - *Scrip*, 9 Mar, 2023.)

At an industry event in India earlier this year, a senior Siemens executive referred to a GSK case study pertaining to the deployment of digital twins for the development and production of adjuvant

technologies – a "real-time capable model" that has the ability to predict adjuvant particle size. Adjuvants are vaccine additives that boost the immune response; they also help lower the volume of antigen needed for each dose of vaccine, facilitating greater supply of these immunization shots when demand spurts.

Q: McKinsey's recent report on Gen AI suggests that it could deliver potential value of 15-25% of operating profits for pharma when deployed across areas like R&D, content for commercial reps, etc. Any early use cases that have demonstrated high value?

A: The use of AI can help accelerate drug discovery and design at unforeseen speed and also enable better customer engagement with use cases across the complete value chain.

We've seen use cases for target identification and lead screening. In silico target identification is the process of using data-driven algorithms to discover novel molecular entities with potential causal links to a phenotype of interest. We have helped a pharma client deploy the clinomics approach, to establish a proof-of-concept genomics platform for a single therapeutic area in less than eight weeks, identified about 200 preliminary variants of interest in the pipeline. These variants were mapped to protein targets of interest in the client's internal datasets, generating an "end-to-end" discovery pipeline. Similarly, deployment of AI-enabled deep learning models helps prioritize hit/lead screening libraries and automate analysis of millions of microscopy images from high-throughput screening assays. These models have significantly

improved screening efficiency - around 80% of hits identified by screening approximately 20-50% of compounds based on virtual screening prioritization.

Then there are use cases for customized scripts or clinical notes by customer segment. Apart from using Gen AI for customer relationship management, creating training modules etc., it also has the potential to create customized communications, scripts and content to match the structure for sales reps leading to high quality interactions with their customers/healthcare providers. It can also be used for speech recognition to help doctors transcribe and analyze their conversations with patients and drafts clinical notes. It is expected that the application of Gen AI within the marketing and sales function has the potential to generate a productivity lift of 4% of global functional spending, or \$490bn.

Q: There's talk around the potential of Gen AI in pharmacovigilance in terms of adverse event identification across multiple sources, real time insights etc. Can Gen AI be effectively trained to recognize facts, fiction and everything in between? For instance, in the COVID-19 vaccines arena there were equal loads of misinformation/scaremongering as there was science-based evidence and some blurring of the lines as well.

A: Pharmacovigilance (PV) requires monitoring the effects of pharmaceutical products, surveillance of known side effects, as well as sifting through large volumes of data to identify and act on emerging, previously unknown side effects. Independent third-party research has shown that an important caveat here is heterogeneity of PV data, that are derived from a multitude of medicines, including vaccines, and, as a result,

describing very different types of adverse drug reactions and adverse effects of vaccines, that have different mechanisms of actions, can be challenging.

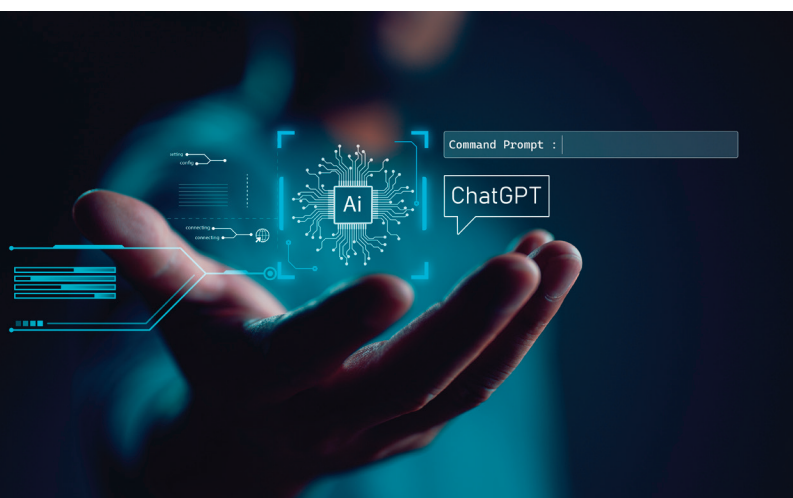
Significant human feedback will be needed to train these Gen AI models using previously analyzed PV data and introduce capabilities to identify unexpected outcomes. There is also an increased need to verify whether generated content is based on fact or inference, thus requiring a new level of quality control.

Gen AI models can be trained to perform PV tasks given the large volume of data, high degree of uncertainty and need to learn from data. This will mean a phased adoption including significant training, building and improving models with increasing accuracy, followed by piloting with data where outcomes are known. After multiple successful "cold" trials, such models can be launched for PV tasks with necessary human oversight.

Q: What about the big grey areas - inherent bias embedded in generative AI data, data privacy/security and IP aspects. (Also see "BioAsia 2023: Leaders from Novartis, Apple Talk Innovation, Tech, Data Privacy" - *Scrip*, 28 Feb, 2023.) (Also see "Artificial Intelligence Legislative Activity To Start In Fall; Sen. Schumer Lays Out Principles, Process" - *Pink Sheet*, 5 Jul, 2023.) Are there sufficient guardrails/effective governance efforts in place or are we looking at a potential flood of litigation?

A: Gen AI has increased the need to understand whether generated content is based on fact or inference, requiring a new level of quality control. Given it is early days for Gen AI, regulations and refinements are needed before Gen AI models based on internet data can be widely deployed.

Hence, regulations surrounding AI and Gen AI are being developed globally and will continue to evolve. These regulations may differ in scope but contain certain denominators such as common principles around transparency, explain-ability, privacy, fairness, accountability, etc. In fact, tech solutions focused on AI risk management to enable compliance and international organizations to advance global standards around AI are also coming up, such as the 2019 OECD Recommendations on AI, the first set of inter-governmental policy guidelines on AI, adopted by 42 countries and supported by the EU, which are influential in international policy setting though not legally binding. While such regulations are coming up, organiza-



tions have also started self-regulation through AI principles and guidelines, strategically keeping humans in the loop and ensuring security and privacy as top considerations for any implementation. Going forward, companies may need to implement new quality checks on processes that shift from humans to generative AI, such as representative-generated emails, or more detailed quality checks on AI-assisted processes, such as drug discovery.

Q: Digital twins in medicine are expected to revolutionize drug development, manufacturing, and the supply chains. (Also see “Indian ‘Lighthouses’ Deliver Gains Amid Price Erosion, Rising Input Costs” - *Scip*, 3 Jul, 2023.) Where do you see things headed in terms of more precise diagnosis, personalized treatments, shorter pharmaceutical processes and informed input-output predictions for biochemical reactions etc.?

A: Digital twin technology has been adopted quite successfully across various functions in the pharmaceutical value chain such as quality control (e.g., automated lab scheduling, prevention of deviations/out-of-specification), manufacturing (for determining optimal changeover settings), supply chain (to predict upcoming bottlenecks through simulation of complex interactions between sub functions) and R&D (mimic process behavior).

As the industry learns and develops these models and the comfort around these grows, we will see deeper application of this technology. For instance, in manufacturing, going forward, we see pharma factories are connected to the IoT [internet of things] and a digital twin of the pharmaceutical production process, and supply chains are accessible from anywhere in the world. We see more reasons to build hubs with control towers to run planning, quality investigations, maintenance support, audits and operational excellence projects, increasing effective capacity by over 10% for planning manufacturing processes.

If we consider supply chain planning and scheduling as the product portfolio of pharma companies continues to grow and diversify, it increases the volatility of the supply chain from sourcing to sales. We have seen the first examples in pharma of digital twins for planning and scheduling. The models mimic all the constraints that exist, such as demand, lead times and equipment capacities, but also shelf life, different market authorizations, number of people on shift on a given day and batch sizes. Today, planning and scheduling activities

which involve 10% of the staff right now can be fully automated in the future. The main benefit, however, will be better utilization of the infrastructure, which currently shows an average utilization of only 40%.

In areas like technical development in R&D, process development and scale-up can be laborious and time-consuming. Chemistry, manufacturing, and controls (CMC) labs are already using digital twin models to mimic process behavior, filter and predefine experimental conditions, reduce the number of wet lab experiments. Digital twins of unit operations will be routinely used to optimize process parameters such as glucose concentration, cell density and acetate level in real time, as well as to select optimal HPLC [high-performance liquid chromatography] columns and predict formulation parameters. Digital twins could be combined into a digital twin of the entire lab, enabling the simulation of complete CMC processes across the value chain.

Q: What's your view on the metaverse and its potential in pharma, including around facilitating cross-border collaboration in medical research by creating easy-to-access virtual environments or generating a virtual patient based on clinical data to predict a specific outcome? Is it much hype for now given issues around the limited interoperability among virtual worlds and governance?

A: Potentially, pharma companies can use the metaverse to deliver enriched, immersive experiences to healthcare providers and patients through multiple use cases. The metaverse has introduced the ability to not only be present within a virtual world but to also engage with that world alongside other users.

However, metaverse applications are still in an early stage of development and use cases will depend on how easily stakeholders are able to adapt these. Before it is used for medical research collaboration or generating virtual patients, proper pathways and regulations need to be put in place. This is expected to evolve as we start seeing gains from successful use case deployment using metaverse.

Areas such as commercial are expected to see faster adoption, given lesser regulatory requirements compared to cutting edge medical research. For example, a medical science liaison could use a 3D model to explain to an oncologist the mechanism of action of a given drug. This could be a significantly higher level of interaction, increasing a pharma company's involvement and engagement with physicians.



Lisa Takagi
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Takeda's Weber On Digitalizing Pharma In Ongoing Strategic Shift

China Now A Top Priority

The entire pharmaceutical industry will transform itself with digital technology while still facing the challenge of financial balance as a part of the healthcare ecosystem, says Takeda's CEO, who shared his views on the firm's and wider industry's shifting business and R&D strategies at the recent CPHI Japan meeting.

Takeda Pharmaceutical Co. Ltd. president and CEO Christophe Weber attracted hundreds of people to his keynote presentation at the CPHI Japan 2023 meeting in Tokyo, where he shared his views on the financial challenges facing the entire pharmaceutical market and hopes for innovation, while referencing his own company's market expansion and technology-focused investment strategies.

In a Q&A session lasting even longer than his 30-minute presentation, Weber shared his opinions on a broad range of topics, including the pharma industry's challenge in finding a good financial balance, ideals for technology and Takeda's own future transformation through the wider implementation of more digital technologies.

The CEO began by describing the current situ-

ation for the global industry as "an extraordinary time," pointing out both the optimism for rapid technological innovation but also the fiscal hurdles, especially in developed countries looking to maintain healthcare ecosystems but facing ever-growing costs.

While Takeda is unusual as a top 10 global pharma firm from Japan, considering its relatively low population size, behind its recent successful growth has been expansion in the huge US market, while also focusing on new and innovative drugs.

Back in the 2014, when Weber joined the company, one of its biggest weaknesses was that "our US presence was too small," he conceded, pointing out that its sales in that market accounted for only 24% of the total at the time, with Japan making up 40%.

Takeda has since expanded substantially in the US, the biggest market for new drugs, to enhance its margin over the last decade to also to pay back its investment in R&D, he noted.

BALANCING SALES AND INVESTMENT

For a firm focused on new drugs like Takeda, in order to manage the balance between sales and continuous investment into R&D for further growth, it was necessary to scale its presence in the US market, where 70% of new drugs are launched, Weber told the session.

"You have to be strong in the US. That's where you get your R&D payback mostly," he noted, although later pointed out that the current worldwide pharma market has been "too dependent" on the single country.

Through a strategic shift including the early 2019 acquisition of Shire and expanding its employees in the US, the ratio of revenue from the country jumped to 48% in 2021 - as did Takeda's total sales, from JPY1,777bn in 2014 to JPY3,569bn (\$26.43bn) in 2021. "By increasing our scale, we almost doubled our margin, which was very important. We also increased our equipment fee in R&D budget," said Weber, noting the firm now invests about \$5bn per year into R&D.



Christophe Weber, president and CEO of Takeda, at CPHI Japan in Tokyo. Source: Lisa Takagi

Now managing a pipeline of roughly 40 new products to stay competitive, the debt of the firm to acquire Shire and enhance R&D have now decreased to a “comfortable level” after several years of effort, the CEO said.

Now providing its products to 80 countries, the next strategic focus market will be China, where “we are growing very fast as well.” (Also see “Takeda Sees Mainstays Tiding It Over Upcoming Expiries” - *Scrip*, 11 May, 2022.)

INVESTMENT IN DIGITAL TECHNOLOGY, MODALITIES, ECOLOGY

Weber pointed out the next driving force to transform the entire industry will be digital technology, including data and artificial intelligence (AI). “We think this is the moment for the pharmaceutical industry to be digitalized. We think that every drug in the company will be changed for the next few years,” he told attendees.

In response to a question from *Scrip*, he admitted that this is one of the biggest challenges that both his company and the wider industry faces today.

“

We always have to move forward. And I say, if you’re not moving forward, you’re moving backward.”

- Christophe Weber,
President & CEO,
Takeda

Takeda is investing around JPY200bn in data and digital technology capabilities in preparation for the expected “revolution” in technology which will transform the sector and lead to massive competition, he noted.

The firm is already using technology to transform its manufacturing processes, R&D and working style, especially since the COVID-19 pandemic. In manufacturing, one example is line clearance after finishing the process for a particular product.

In one of its factories in Japan, every line clear-

ance “used to take one hour with three operators going pole-to-pole to check everywhere if there were tablets or something in the line,” said Weber. But after installing a digital system with cameras, the process was shortened to just three seconds.

Weber expressed a wide range of expectations for how digital technology can change both R&D and therapeutics after products are marketed. Using data can reduce R&D costs by shortening the process of patient recruitment for a clinical trial, for example. He also pointed out that digital technology will be a companion “to every molecule” released by Takeda, for instance through inclusion in diagnosis and monitoring procedures, which would benefit doctors, patients and pharma firms.

Weber noted Takeda has already been running a pilot program for Crohn’s disease (for which it markets the blockbuster biologic Entyvio (vedolizumab)), which would “change the pattern of the treatment” by predicting symptom crisis for each patient.

EXPANDING ACCESS

While Takeda has been putting its focus on “life-changing” new drugs, Weber also stressed it has been making efforts to improve product access in developing countries by controlling offering prices. One example is the dengue vaccine Qdenga, for which the firm received a first approval globally in Indonesia last year.

Now also available also in Brazil and Europe, the quadrivalent product is “the first truly innovative, effective and safe dengue vaccine that’s been a 10-year project,” the executive told the CPHI meeting, organized by Informa Markets. (Also see “Global First Approval For Takeda’s Dengue Vaccine, In Indonesia” - *Scrip*, 24 Aug, 2022.) (Also see “Dengue Vaccine Qdenga & Nine Drugs Win EMA Thumbs Up” - *Pink Sheet*, 17 Oct, 2022.)

The firm launched the vaccine for \$46 par dose in Indonesia, while in Germany it had a much higher price of \$85. Admitting even the lower price “is still high for Indonesians,” it has nevertheless been kept low for an innovative vaccine, Weber pointed out. He expressed the hope that Takeda’s ongoing investment in digital technology will eventually result in more effective processes with lower cost.

“I think we need to be ready for more business coming for emerging countries,” Weber said at the end of his session, answering an audience question about making the company’s products available in developing countries.

“That’s why in the long term, we need to develop new medicines at lower cost. It’s too expensive to develop a medicine. I think technology and data, AI will reduce the cost of R&D of molecule. It has to.”



Merck Life Science leaders Aditya Sharma (left) and Tathagata Ray (right) share views with *Scrip*.

Source: Merck



Vibha Ravi
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Merck Life Execs On APAC Firms' mRNA Tech Readiness, Start-Ups And AI

VCs Lack Understanding Of Biotechs

Merck Life Science's top executives in India tell *Scrip* how they are helping biologics companies in APAC on their mRNA therapy journey. In the wide-ranging discussion, use of AI, the startup environment for biotechs and the changing face of manufacturing in India also came up.

Top executives of Merck Life Science, Merck KGaA's arm offering research and manufacturing products and solutions for chemical and biological drugs, in India say "almost everyone" in the biologics space is looking to build mRNA platforms, with their customers being at varied stages in this journey.

Japan, China, South Korea and India are some of the large countries within APAC where "we see a lot of interest in mRNA.....[with] almost everyone looking to build mRNA platforms whether for vaccines or other therapeutics," Merck Life Science's

head of bioprocess business for India region, Aditya Sharma, told *Scrip*.

However, "the degree of thinking and investments are different because the know-how is different. So, I would say Japan, Korea and China are ahead because I think they were working on this before India," Tathagata Ray, lead for global commercial strategy and development, said during the interview adding that the manufacturing infrastructure in India needs to be upgraded.

"There are many promising technologies for the future, but mRNA [technology] manufacturers can take on rather riskless," given that the technology is not new even though it is currently a buzzword, with acceptance for mRNA products having improved significantly since COVID-19 vaccines were launched by Pfizer Inc./BioNTech SE and Moderna, Inc., Ray said.

Merck's life science business, which operates as MilliporeSigma in the United States and Canada, has capabilities in almost every step of the 16-17 step process of making mRNA products with a wide range of offerings, Sharma said adding that Merck's acquisition of AmpTec, a Germany-based mRNA contract development and manufacturing organization, in 2021 proves that Merck began taking this technology seriously some time back.

In India, Merck Life Science has worked closely with Gennova Biopharmaceuticals Ltd via its science and lab solutions business. Gennova recently launched Gemcovac-Om, an Omicron-specific version of its COVID-19 mRNA vaccine, which is to be used as a booster dose. It's distinct from other mRNA vaccines in not requiring ultra-cold chain infrastructure and in its delivery via a needle-free injection device. (Also see "CEO Of India's mRNA Pioneer Gennova On Cancer Vaccines, VC Interest" - *Scrip*, 27 Jul, 2022.)

Merck's Science and Technology Team works very closely with customers to help them scale up, develop and manufacture these products and the company is changing some of its approaches along the way, Ray said.

"The industry together is learning. A lot of collaboration is going on and we are also changing some of our approaches because most of the raw materials we supply are for MABs [monoclonal antibodies] and vaccines. The requirement of mRNA is a little different. So, for an example scale will only be several thousand liters of bioreactors for the CDMOs, CMOs worldwide. Also, since turnaround is faster, single use will get high priority," he added.

Asked if India's vaccine majors like Serum Institute of India Pvt. Ltd. and Bharat Biotech are also looking at developing mRNA products, Ray said "any investment happens where the money is. So, if companies keep making old generation vaccines, they can have a share of 25% of all the manufacturing in the world, but they will not get into the list of top 10 in revenue. So, if you have to be profitable, you will have to come to technologies which are new and more effective."

HOW TO FIRE UP BIOTECH START-UP ECOSYSTEM

The executives also expressed views on what's needed to fire up India's biotech startup system, saying apart from funding, academic culture and curricula that drive innovation and an enabling intellectual property (IP) environment, professionals should have the freedom to question and correct existing practices.

When *Scrip* pointed out that ample funds have been made available by venture capital (VC) and private equity (PE) firms to food and education

entities like the now beleaguered Byju's while Indian biotechs continue to face funding pressures, perhaps due to longer gestation periods, Sharma said COVID-19 showed "how quickly we can scale up some of these technologies, how fast you can get the return on your money."

Talks with senior executives at such funds reveal that "many of these VCs probably don't understand this space. So that's why money's not really flowing. VCs are putting money into food and grocery apps, which are just burning money for the last five years maybe and having this valuation which doesn't mean anything."

“

Automation was never a very big thing in the pharmaceutical world, I think that is changing pretty quickly. Five years back we thought one cloud and one platform with machines operating in tandem while talking to each other could be a reality, maybe after 10 years. But now it looks like it is much faster.”

- Tathagata Ray, Lead for Global Commercial Strategy and Development, Merck Life Science

Asked if venture capital firms' impatience with returns might also be a factor, he said "I think many of these investment bankers are ready to wait if they know after five years whether their money is going to get doubled, tripled or whatever, but that's missing right now." (Also see "Pfizer's India MD On Funding Healthcare Startups" - *Scrip*, 11 Apr, 2022.)

Asked by *Scrip* if China's model of encouraging professionals employed outside the country to return and start companies could work for India as well, Sharma said traditional ways of thinking and systems need to evolve.

"If you are a very successful executive in the US or Europe, what motivates you to come back? Money is definitely one thing at that level," saying start-ups might not be able to afford to pay the salaries these executives get, but the governments in a few countries reimburse fully or partially such executive compensations.

However, "can these companies build a culture where they can take what the executive is bringing back? For example, these executives might challenge the owner of the organization and say you need to do things this way. Can the owner take that and say, "let's change the whole thing, or change the culture?,"" he questioned.

50-70% SAVINGS FROM CONTINUOUS MANUFACTURING

The executives also pointed to the change in India's production processes with the adoption of new technologies for mRNA and continuous manufacturing.

Incorporated in India as E. Merck India Pvt Ltd in 1967, Merck KGaA has about 56 years of experience of running the pharmaceutical, healthcare, life science and electronics business in the country and its executives have seen the manufacturing landscape evolving. (Also see "Merck KGaA Expects Modest Growth Ahead Of Launches Next Year" - *Scrip*, 2 Mar, 2023.) (Also see "Merck KGaA Stepping Up In India, Eyes On Bavencio Trajectory" - *Scrip*, 6 Sep, 2021.)

"Automation was never a very big thing in the pharmaceutical world, I think that is changing pretty quickly. Five years back we thought one cloud and one platform with machines operating in tandem while talking to each other could be a reality, maybe after 10 years. But now it looks like it is much faster," said global strategy lead Ray.

Companies could end up with savings of "somewhere in the bracket of 50 to 70%," with automation, data gathering and continuous manufacturing helping to bring down the recurring cost of production, he added.

However, "continuous processing is not for every molecule in the world" given that it needs continuous demand and supply. In addition, companies which have already invested in batch processing would not find it easy to make the switch since "all your hardware is already fixed" and continuous processing works in an entirely different way compared to batch processing.

Asked if product recalls become more difficult to achieve if continuous manufacturing is adopted, Sharma said there have been questions around what constitutes a batch in this kind of production. "So, if you say the entire year I have produced one batch that's a challenge. Those are the things that we are trying to address, and customers are also thinking about that."

Besides, other regulatory aspects around continuous processing need to be addressed. "I think there were some regulatory questions around it. That's why people are still waiting as to how do we answer some of those. Like what is a batch in a continuous processing? How do you qualify data, what kinds of data requirement are there?"

USE OF AI IN CLINICAL RESEARCH

The executives also spoke about the benefits of using artificial intelligence (AI) and machine learning (ML). To *Scrip's* question on their use and particularly their scope in India, Sharma said "I see lots of utilization of AI and machine learning particularly in clinical trials."

"You will need to get enormous amount of data, right? And then make sense of it. If you have the right kind of AI to just feed data and that tool has already millions of billions of data points fed in, then it can tell you whether this drug is going to be effective or safe or not. But, as more and more data are fed into these tools, I think the predictive validity will be much, much more credible."

Ray also spoke about how use of AI can prevent animal testing in the preclinical stages. "As you know, of 50 candidates, only one will enter the preclinical data frame. So that means a lot of data gets generated as input on those 50 candidates, of which only one comes to clinic."

Talking about imaging and diagnostics solutions, Sharma said "I was reading somewhere that machines can give up to 99.9% predictability in diagnosis which is much, much better than a doctor. It could just scan your eyes and tell you if you're going to get diabetes in the next 10 years because it already has billions of data points."

As the use of AI and ML increases, "predictability gets better. So, it would be interesting to see how it works out," he concluded.



Jung Won Shin
Senior Editor

TPD A Rising Option For Korean Pharma Seeking New Modalities

SK Biopharm Making Aggressive Move

Highlighted by SK Biopharmaceuticals' recent decision to acquire the US-based ProteoVant Sciences, Korean pharma firms are stepping up deals and collaborations in the hot TPD space, which is expected to continue to attract global investors and big pharma interest.

Targeted protein degradation (TPD) is becoming a popular choice for Korean pharma firms looking for new drug modalities and growth engines. They are making diverse moves, largely seeking R&D collaborations, M&A and investment.

Among them, SK Biopharmaceuticals Co., Ltd, an affiliate of SK Group, has made a strong move; it has announced the purchase of a 60% stake in ProteoVant Sciences Inc. from Roivant Sciences Ltd., to diversify into the emerging TPD business and boost its oncology pipelines, in a deal worth \$47.5m.

ProteoVant exploits the ubiquitin-protease system (UPS) to discover and develop transformative medicines for the treatment of patients with life-altering diseases. Protein degradation harnesses the human body's innate cellular machinery by way of

the UPS to identify and mark disease-causing proteins for destruction. This "promising" approach provides the opportunity to target proteins of interest, many of which were previously considered undruggable. ProteoVant integrates its degrader drug hunting expertise, MOPED molecular glue screening platform, and external partnerships to advance novel protein degraders across a range of therapeutic areas.

The latest acquisition will make ProteoVant a wholly owned subsidiary of SK Group as SK Inc. already owns a 40% stake in the US firm. Roivant and SK Inc. are founding investors of ProteoVant.

The deal follows SK Biopharm's collaboration with Ubix Therapeutics, Inc. in 2022 to develop new compounds and medicines for potential treatment of cancer. The two companies will develop anti-cancer treatments by using Ubix's Degraducer platform technology. Degraducer is a next generation inhibitor technology that enables targeting of disease-related targets that were previously undruggable.

ONE OF "HOTTEST" AREAS OF GROWTH

Korean firms such as SK Biopharm are keenly looking for opportunities in the TPD segment an area that has been gaining attention as a new modality across the industry globally, with advantages such as specificity for intracellular targets, penetration of cell membranes and the blood-brain barrier and ability to address previously undruggable targets.

Multinational firms such as AstraZeneca PLC, Roche Holding AG and Sanofi are actively pursuing development, while Japan's Astellas Pharma, Inc. chose to highlight its growing R&D activities in the hot area of TPD at its R&D meeting, apparently becoming the first major Japanese pharma firm to disclose a strategic focus on the increasingly competitive field.

In April, a potential \$2.55bn multi-year deal was reached between Proxygen and Merck & Co., Inc. to jointly identify and develop molecular glue degraders against multiple therapeutic targets.

"Targeted protein degradation is one of the hottest areas of growth within the R&D pipeline at the moment. The number of assets under development has risen more than sixfold in the last five years, now totalling almost 250 active programs. This rate of growth is even faster than gene editing and mRNA, despite the technology being relatively immature in terms of clinical development," Daniel Chancellor, Thought Leadership Director at Citeline, told *Scrip*.

In addition, significant VC financing in 2022 went to early-stage biotechnology firms developing new modalities aimed at the most challenging disease targets. Developers of new approaches to TPD, such as proteolysis targeting chimeras (PROTACs) and molecular glues, have attracted considerable investment, according to David Dunn, Principal Consulting & Analytics, Evaluate.

"These are today's "hot solutions" to the target-druggability challenge. These new technologies have also caught the attention of large pharma, and many partnerships have been executed."

In spite of the interest and promise, none of these new drugs have yet been approved. The TPD field is reaching an inflexion point, and we expect to see important milestones coming in 2023 and 2024, Dunn told *Scrip*.

OTHER KOREAN TPD COLLABORATIONS

Other Korean pharma firms have also been pursuing partnerships and in-licensing deals of TPD technologies with Korean biotechs, but more acquisitions could be on the horizon as top Korean firm Yuhan Corporation considers M&A as an option, pursuing Korean or overseas targets with great technology and pipelines, and can generate synergies. (Also see "No Future Without New Drugs": Yuhan CSO

On Open Innovation Strategy" - *Scrip*, 26 Jul, 2022.)

Yuhan has reached a co-research and development deal with UPPTHERA Inc. for Alzheimer's disease and anti-inflammatory drugs is a starting point and there are plans to expand efforts to secure in-house technologies and co-development. The pharma firm is seeking opportunities to access proprietary platform technologies, with a focus on new modalities such as TPD.

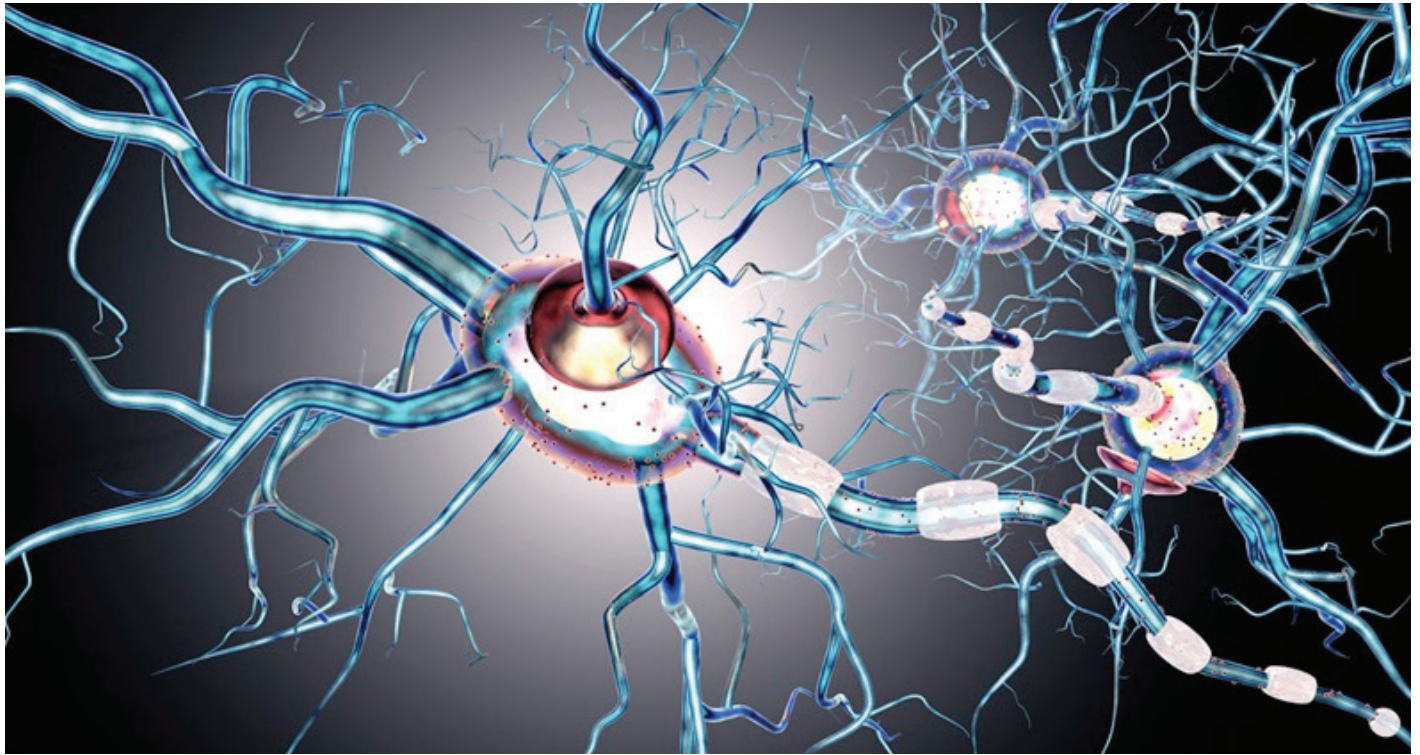
UPPTHERA's novel E3 ligase platform is designed to efficiently degrade the disease proteins on ER membrane, while UPPGRADER platform is its expression-based platform which can deduce a customized set of E3 ligase(s) harboring tissue or cell-type specificity. Through analyzing the tissue proteomics/RNA-seq and normal/disease scRNA-seq expression data, the platform can select E3 ligases which could be specifically expressed in disease-causing or modifying cell types with less anticipated on-target toxicity.

The biotech has also reached an agreement with Boryung Corp., formerly Boryung Pharmaceutical Co., Ltd., to co-develop a new drug in multiple myeloma and aims to out-license the early discovery stage TPD pipeline to a third party including multinational pharma.

In addition, Daewoong Pharmaceutical Company Ltd. has reached a co-development agreement with Pin Therapeutics to discover new TPD drug candidates. Pin Therapeutics has been focusing on the development of TPD technology and is developing two types of drugs: PROTAC and Molecular Glue Degradator. PROTAC and Molecular Glue Degradator act by similar mechanisms to degrade target proteins but have different properties in terms of compound structure, drug properties, and ease of selection of target proteins.

GC Biopharma Corp. has similarly linked with Cyrus Therapeutics, Inc. for the development of TPD drugs. Cyrus primarily focuses on developing small molecule medicines to conquer 'undruggable' cancer targets and expanding new chemical spaces such as targeted protein degraders and antibody recruiting molecules. It is targeting difficult-to-drug proteins in multiple oncogenic pathways associated with RAS/MAP kinases, DNA damage response, cell cycle and transcriptional regulation, with an emphasis on synthetic lethal targets. It is also pursuing a small molecule-driven approach toward immunotherapy.

Despite the still weak sentiment in the VC financing market, some Korean bioventures with TPD technologies have raised sizable funds in the first half amid strong investor interest in the sector. Ubix Therapeutics has raised KRW12bn (\$9.2m) in a series C, while Orum Therapeutics has raised KRW26bn in a series B.



Brian Yang
Managing Editor

Rare Opening In Tough Times: New Biotechs Rekindle CNS Development In China

But Regulatory Barriers Remain

After leading a Nasdaq-listed Chinese biotech, I-Mab Biopharma Co., Ltd, as CEO for years, Joan Shen has started and is CEO of her own new bio-venture, NeuShen Therapeutics, which is focusing on central nervous system conditions.

The first target disorder for the Shanghai- and Lexington-based startup is amyotrophic lateral sclerosis (ALS), a rare and rapid progressive neurodegenerative condition. The Shanghai firm has already closed an initial pre-A round funding of \$20m from a group of Chinese investors and opened an R&D center in the US, and is collaborating with the University of Massachusetts.

The academic partnership will focus on an adeno-associated virus-based gene therapy for the condition and the new company also intends to develop small molecule drugs for ALS.

Shen is not alone in taking the plunge with a new venture, however, and is just one of many

high-level returnee pharma executives who have started their own biotechs in China over the past few years and concentrating on rare CNS conditions, although the majority of such operations are devoted to cancer.

At least 22 companies have flocked into CNS drug development in China, among them NeuExcell. NeuExcell Therapeutics Inc. whose chairman is former Novartis AG China president Yin Xudong. Another, 4B Biotech, was founded jointly by former GSK plc China R&D vice-president Guan Xiaoming and Tsinghua University professor Lu Bai.

APAC AS A SITE FOR CNS R&D

Given the emerging new modalities of mRNA and gene therapy, rare CNS conditions such as ALS are moving into the spotlight, not only in China but in Asia Pacific as a whole.

Seizing the opportunity to bypass conventional

small molecules, Chinese biotechs are also betting on partnerships with leading researchers in the US to accelerate development. Professor Guo Guangping, a leading expert on AAV families for use in gene replacement therapies, is sought after not only by CNS developers but also other firms working on rare diseases in China.

Elsewhere in APAC, Japanese drug makers are leading regional CNS development, with Eisai Co., Ltd. having obtained multiple approvals in the field, including in the US for Alzheimer's disease drug Leqembi (lecanemab). Otsuka Pharmaceutical Co. Ltd., meanwhile, is a leader in schizophrenia and psychiatric disorders, with its blockbuster Abilify (aripiprazole) franchise.

In South Korea, local companies are active in gene and cell therapy, including ViroMed Biopharma, which has started trials for donaperminogene seltoplasmid, a gene therapy for ALS.

Around the APAC region, 116 trials have taken place for ALS over the past decade, led by Japan and followed by China, which is quickly emerging as a center for global CNS research (see dynamic infographic above). Data from Citeline's Trialrove show that a total of 22 trials have taken place in the country for the condition over the 2013-22 period, run by a variety of multinationals and domestic firms.

SPEED IS KING

Amid the blossoming CNS research in China, there is also anxiety around additional and sustained financial support, which is looking increasingly uncertain given the global biotech funding challenges. Bioventures taking assets into the clinical stage face skyrocketing costs and a need for ongoing funding and must not rest on their laurels to compete, especially given long development times and uncertain regulatory approval, executives told *Scrip*.

The US approval of Amylyx Pharmaceuticals, Inc. Relyvrio (sodium phenylbutyrate/taurursodiol) for ALS last October has provided other global impetus to the sector, although this was not without some

controversy given a strong lobbying presence for the disease in Washington.

So far no gene therapy has gained approval for the disease and APAC is also lagging in venture capital funding for CNS, which makes sustained support for the slew of new startups uncertain.

In China, aside from traditional Chinese medicines, several ALS drugs including edaravone, developed by Japan's Mitsubishi Tanabe Pharma Corporation and domestically by Nanjing Yoko BioMedic, have been approved.

However, even local patients are still looking for more effective treatments and a gene therapy with the promise of curing the condition has many excited about the possibility.

So far, Chinese biotechs seems to be betting on quickly entering into the preclinical/clinical stage to accumulate data and executives at the recently founded companies say the winning recipe will be to rapidly build up the pipeline.

A recent multimillion dollar deal between Bi-onTech SE and Durality Bio in Suzhou has many believing that as long as there is true innovation, there will be potential buyers or licensees. Executives are hoping a good pipeline will help secure funds, although the overall capital crunch may work against them.

Even some more established gene therapy developers such as Belief Biomed Inc., which has a clinical-stage therapy for hemophilia A, are scrambling for cash.

REGULATORY BARRIERS

Apart from funding and R&D anxiety, the new set of biotech founders see remaining regulatory hurdles for gene and cell therapy developers.

Given that they are founded mainly by Chinese American returnees, the companies, - according to current Chinese regulations - may face challenges to enter gene-related development due to strict rules around the field. Under China's opaque human genetic resources management regulations, foreign companies must register, file and get approvals prior to collecting, storing and using human samples.

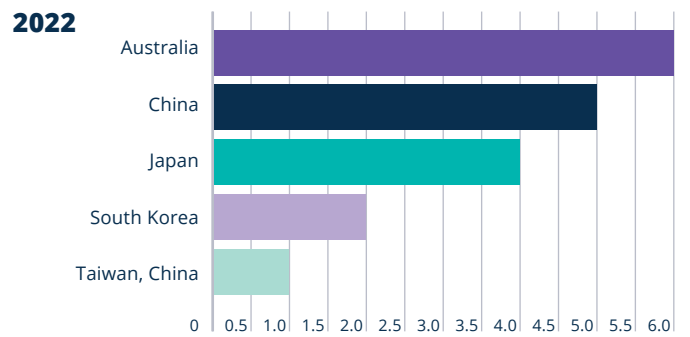
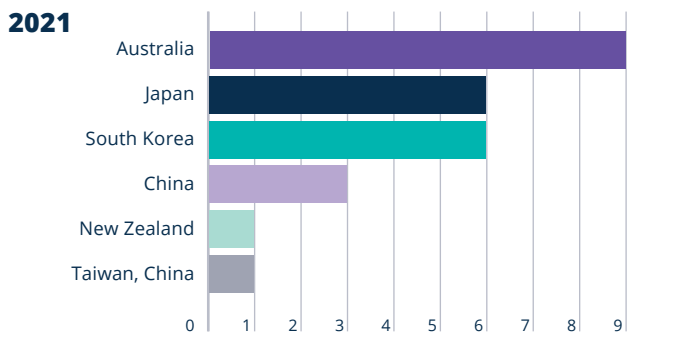
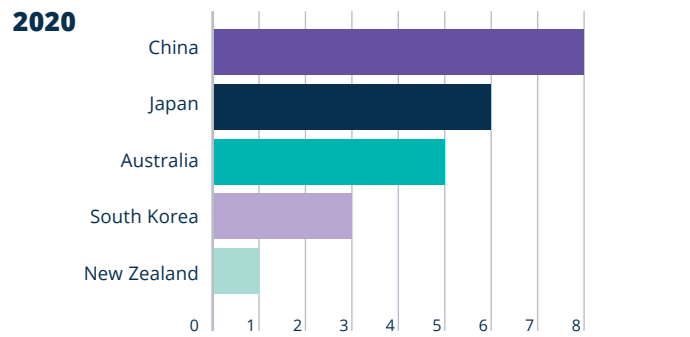
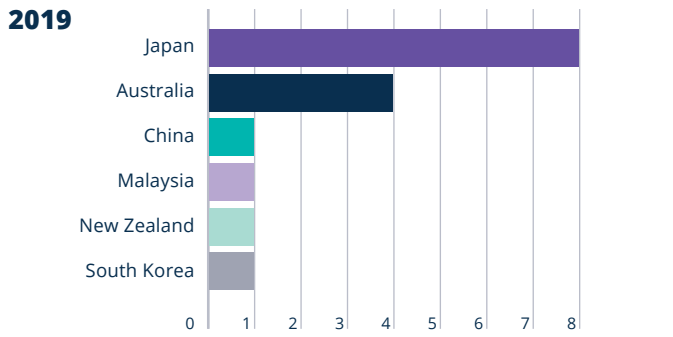
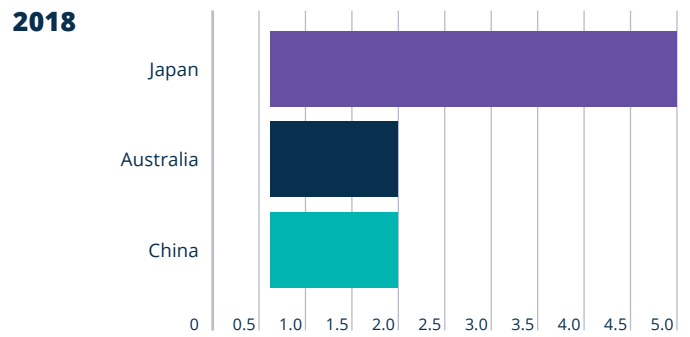
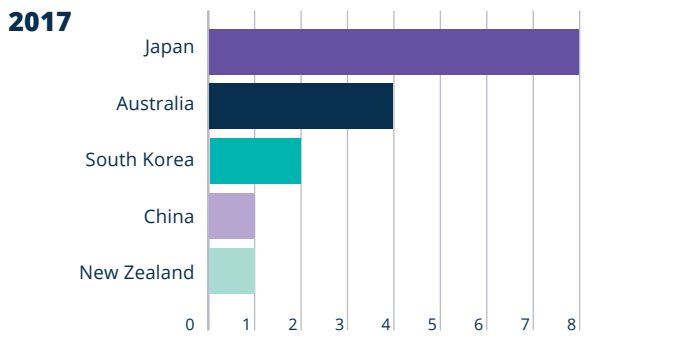
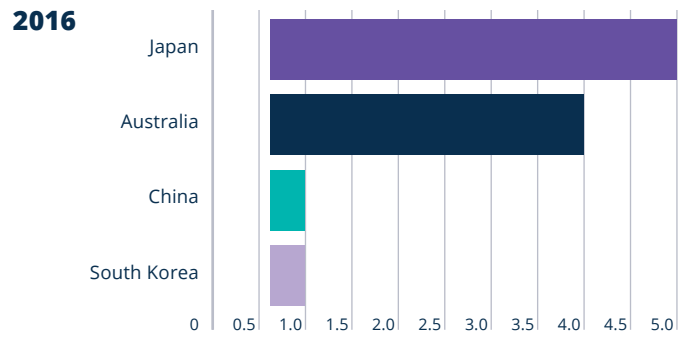
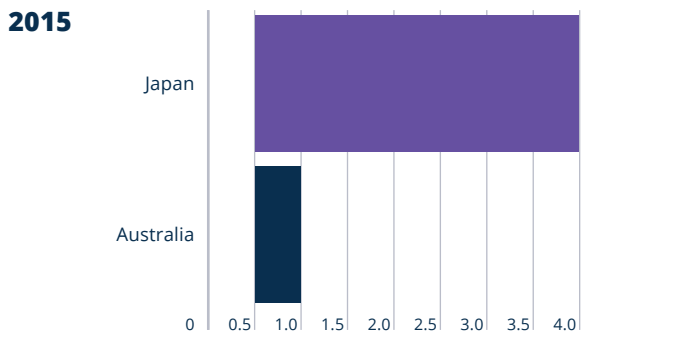
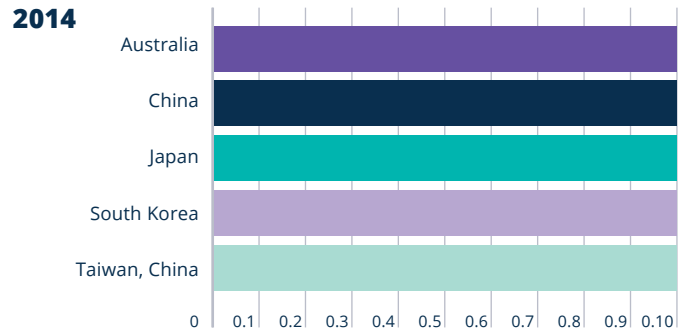
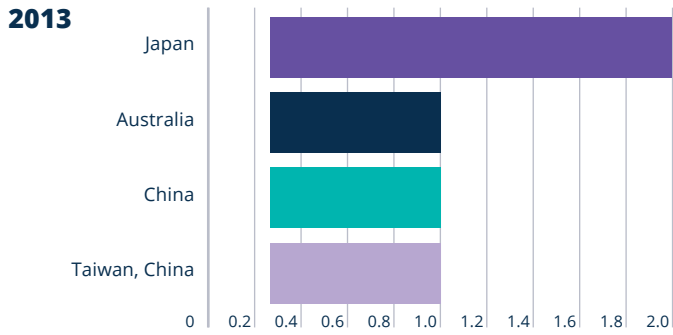
In a tit-for-tat tactic to respond to Washington's restrictions over the export of key technologies to China, Beijing is also banning gene- and gene editing-related technology exports, which could further complicate the prospects for some developers.

But the flip side is that recent regulations to encourage rare disease drug development in China, issued by the Center for Drug Evaluation, give pediatric and rare condition treatments a specific timeframe in which developer can be expected to have communications with regulators.



APAC CLINICAL TRIALS FOR ALS DRUG DEVELOPMENT 2013-2022

Source: Data from TrialTrove



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