WHITE PAPER

JAPAN AND CHINA ARE OUTPACING EUROPE AS LEADING BIOPHARMACEUTICAL INNOVATION HUBS

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The development and commercialization of novel biopharmaceutical products in recent years has continued to offer more safe and efficacious treatment options for patients across therapeutic areas. While a good proportion of the world's transformative drug development and early commercial resources for novel therapies are focused in the United States, the level of drug innovation in the rest of the world has begun to shift. In the past decade, Japan and China have invested in regulatory reform and established policies to increase drug innovation within their respective countries. Quantitative metrics of geographical commercial attractiveness and domestic drug innovation between 2015 and 2021Q1, indeed, support an acceleration of innovation in the Asia-Pacific region. More biopharma companies are launching novel drugs in Asia-Pacific first and the ambitions of China as a major developer of branded biopharmaceutical products is coming to fruition. The global drug innovation tide is picking up in the East and both Japan and China are poised for a sustained position as global leaders.

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INTRODUCTION

It is no secret that the US is the largest and, often, most attractive market for developing and commercializing novel biopharmaceutical products. Companies can command strong prices after successfully navigating well-established regulatory pathways and securing reimbursement from major payers. Furthermore, the scientific talent and widely available funding for early stage biotechs makes the US one of the most attractive biopharma innovation hubs in the world.

While the US is a clear leader, there is growing contention for the second most innovative and attractive commercial drug market in the world. What's your gut instinct for the next ripest market to develop and commercialize a novel therapy? For those in the West, the gut intuition is likely Europe, or specific countries within the highly fragmented region. For those in Asia-Pacific, perhaps Japan came to mind or China and its population of 1.4B.

In recent years, Health Advances has been observing shifts in global dynamics, as domestic innovation in Asia-Pacific accelerates and Western companies increasingly look East. So, we asked ourselves whether quantitative measures of drug innovation indeed support changing sentiment for the second most attractive major market for novel therapies.

Here, we investigate how quantifiable measures of drug innovation have changed in the past 5-6 years and if Asia-Pacific countries have begun to overtake Europe's legacy position as the second most innovative biopharmaceutical market.

In this article, we explore shifts in global drug innovation between 2015 and 2020Q1 using the following metrics:

- **Geographical commercial attractiveness** by investigating in which country or countries drug developers **first launched** novel biopharmaceutical products
- The level of **domestic drug innovation** by evaluating the number of novel drug launches by **company headquarter region**

Additionally, we will walk through recent underlying regulatory, market access, and funding trends that have led to recent drug innovation changes and implications for future launches of novel agents.

METHODOLOGY

We used the drug database Citeline PharmaProjects to identify 234 novel therapies launched between 2015 and the first quarter of 2020. In this study, "novel drugs" excludes vaccines and are defined as new active substances (NAS), including regenerative medicines, that are not reformulations, imaging agents, infectious disease immunizations, or environmental allergy immunotherapies (see appendix for detailed methodology).

We split the launched novel drugs into two cohorts based on each drug's first launch date, as reported by PharmaProjects: 2015-2017 and 2018-2020Q1. Each of the cohorts is comprised of a similar number of launched drugs (118 and 116, respectively) and has a comparable distribution of the most common therapeutic areas (Fig 1).

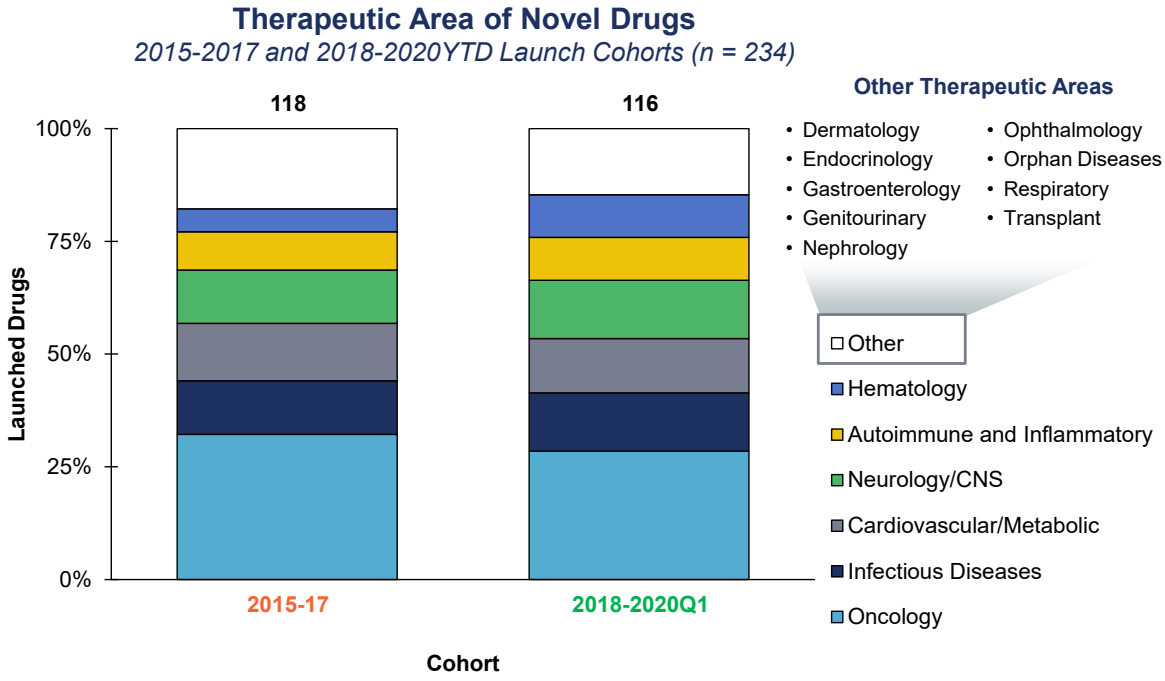


Figure 1: Novel Drug Launch Cohort

To evaluate shifts in commercial attractiveness and domestic drug innovation, Health Advances compared the geography of first commercial launch and company headquarters for drugs within each cohort. We used PharmaProject's designations for the country or countries of first launch. For any drug not solely commercialized by its developer, we determined the primary agent "owner" based on PharmaProjects commentary. We assigned headquarter locations based on the "owner" as of April 2020 and defined the sizes of the companies based on 2019 revenues reported by ThomsonOne Refinitiv:

- "Top 20" companies are defined as those with >$5B revenues
- "Large" companies are defined as those with $1-5B revenues
- "Smaller" companies are defined as those with <$1B in revenues or no publicly reported revenues

COMPANIES ARE INCREASINGLY LAUNCHING NOVEL DRUGS IN JAPAN AND CHINA FIRST, PRIMARILY AT THE EXPENSE OF FIRST LAUNCHES IN EUROPE

Pursuing leadership in global healthcare innovation, Japan and China have established regulatory pathways and reformed market access landscapes to favor innovative drugs

The Japanese and Chinese governments and, in turn, their regulators have made concerted efforts to entice biopharma companies to develop and launch innovative drugs in their respective countries (Fig 2).

Figure 2: National Drivers of Drug Innovation in Japan and China

Japan is known for placing an early emphasis on regenerative medicines, creating a separate regulatory category from pharmaceutical products in 2014 [Tobita 2016 Regen Ther]. However, the country's emphasis on medical innovation extends beyond cell and gene therapies. In 2013, the Ministry of Health, Labour and Welfare (MHLW) established the **Sakigake Strategy** to improve Japan's position as a world leader in the "practical application of innovative medical products" [MHLW Strategy of Sakigake 2014]. **Sakigake** roughly translates to "pioneer" or "forerunning initiative" and is one component of the government's broader "Japan Revitalization Strategy."

One key element of the **Sakigake Strategy** is the creation of the **sakigake** designation for clinical-stage pharmaceuticals, medical devices, and regenerative medicines. Similar to an accelerated approval designation like Fast Track or Breakthrough in the US, the **sakigake** designation aims to advance transformative therapies through favorable regulatory agency access and accelerated review timelines (Fig 3). However, one requirement in particular may be contributing to companies re-directing innovation and commercial resources specifically to Japan: the need to file for approval in Japan before any other country, or "Japan First" as a global launch geography.

The MHLW assigned the first **sakigake** designations to five pharmaceutical agents in October 2015 and three regenerative medicines in February of 2016. Twenty-four additional therapies were granted the designation between 2017 and 2019. To date, seven of these **sakigake**-designated therapies have been approved, including Roche's neurotrophic tyrosine receptor kinase (NTRK) cancer therapy

Rozyltrek (entrectinib), Shionogi's antiviral Xofluza (baloxavir marboxil), and Novartis' spinal muscular atrophy gene therapy Zolgensma (onasemnogene abeparvovec-xioi).

Sakigake Designation Process

Criteria	• ***Innovative***: novel mechanism of action • ***High unmet need indication***: serious/life-threatening condition or condition with persistent symptoms with no other curative treatment • ***Strong efficacy/safety profile***: highly effective treatment that is expected to significantly improve safety or efficacy compared to existing therapies • ***Approved in Japan first***: sponsor must *file for approval* in Japan first
Benefits	• PMDA prioritized consultations • Pre-application consultation • Prioritized review aiming for total review in 6 months • Assigned a concierge manager • Ability to extend reexamination period of post-marketing safety measures • Eligibility for 10-20% price premiums

Figure 3: Sakigake Designation Overview [Maruyama 2018 Bioinsights]

Similarly, policy changes in China were intentionally designed to open up the market more to novel and innovative therapies. The Chinese government has demonstrated its commitment to pharmaceutical innovation moving forward, as is apparent through initiatives such as "Made in China 2025" and "Health China 2030." From a regulatory perspective, the National Medical Products Administration (NMPA, formerly the CFDA) introduced accelerated approval pathways in the past five years, including a priority review designation and fast-track status for drugs developed overseas.

However, the most influential policy change encouraging commercialization of novel therapies in China is probably the rapid expansion of the national reimbursement drug list (NRDL) and provincial drug lists which have rapidly expanded access to recently approved therapies. If a firm is willing to negotiate down prices significantly, drug developers can unlock coverage to one of the largest national healthcare systems in the world.

Drugs launched first in Japan and China increased in the recent years, as agents have advanced under new regulatory and market access landscapes

The location in which companies chose to first launch novel drugs before and after 2018 supports the initial success of Japan and China's innovation initiatives of the past decade.

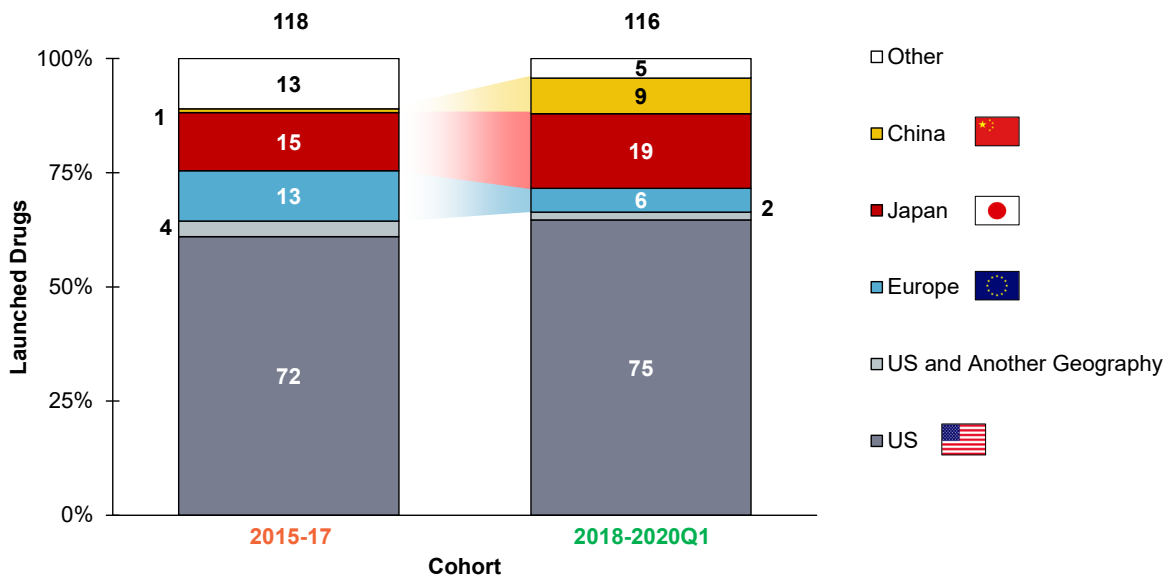


Figure 4: First Launch Geography of Novel Drugs

Unsurprisingly, the US has remained the most attractive initial commercial market for novel drugs, comprising about 65% of first drug launches in the past 5-6 years (Fig 4). However, Japan and China increased in popularity as the geography of first drug launch between 2015 and 2020. Japan remained the second most common geography, but the number of novel drugs launched first in Japan grew more than 25% from 15 launches between 2015 and 2017 to 19 launches between 2018 and 2020Q1. Novel drugs launched first in China grew dramatically between the two time frames driven by domestically developed agents, from a mere 1% to 8% of global new launches.

Meanwhile, novel drugs launched first in Europe dropped more than 50% between the two cohorts, with only 6 first launches in the region between 2018 and 2020Q1. While multiple factors are at play, market access hurdles are a major contributor. In the largest European markets of France, Germany, and the UK, clincial data at launch is often insufficient to merit higher drug prices and a priority review through the European Medicines Agency's (EMA) designation scheme, PRIME, cannot be coupled with market access in member countries to expedite adoption of newly approved treatments.

Approvals by mid-sized Japanese biopharmas have accelerated, as sakigake and other initiatives have begun bearing fruit

The uptick in first launches in Japan was primarily driven by a dramatic increase in domestic drug launches, which grew from 5 to 13 in 2015-2017 and 2018-2020Q1 cohorts, respectively (Fig 5). Novel pipeline agents of both large established companies, like Astellas and Daiichi Sankyo, and smaller Japanese companies, like ASKA Pharma and Kowa, reached the market in the latter time frame. Even though fewer Western companies launched novel drugs in Japan first, the significant growth in domestic launches between the two cohorts yielded a net increase of ~25% across geographies in the 2018-2020Q1 time frame.

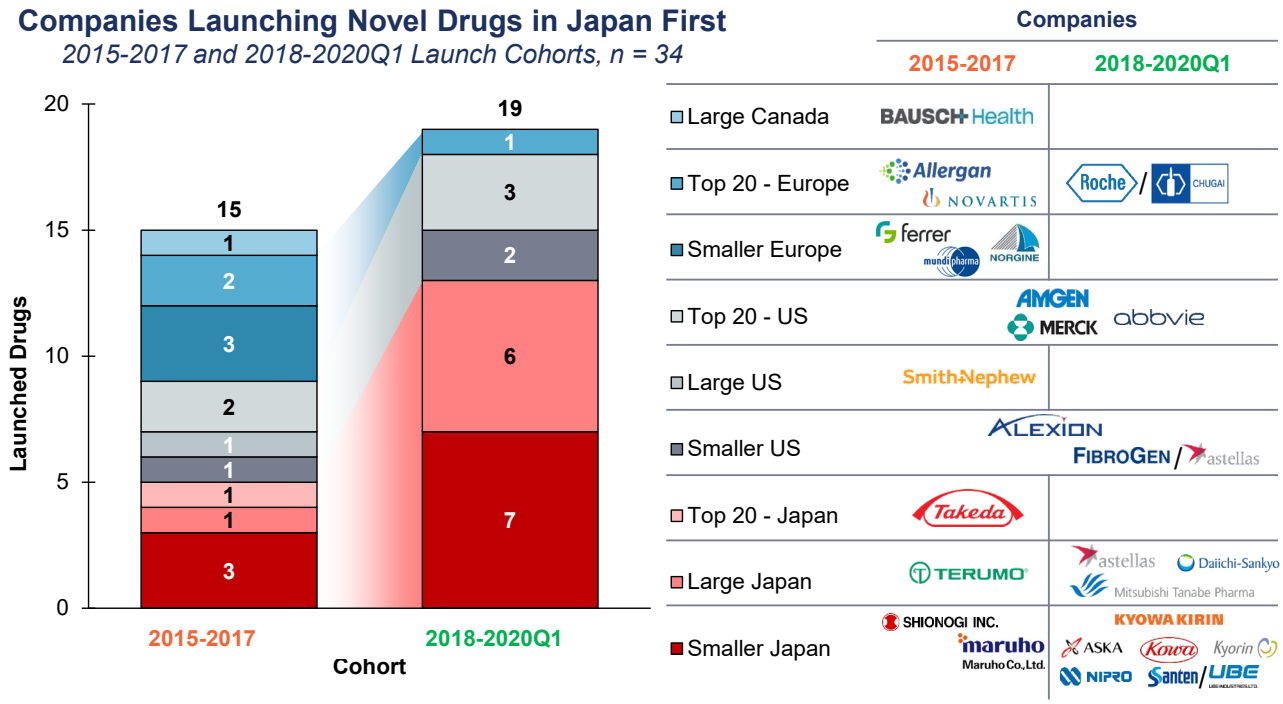


Figure 5: Companies Launching Drugs in Japan First

Additionally, Japan's commitment to drug innovation began paying off between 2018 and 2020Q1 with five **sakigake**-designated drug launches from domestic and multinational companies (MNCs) alike. These marketed drugs span a variety of therapeutic areas, from oncology to infectious diseases and rare diseases:

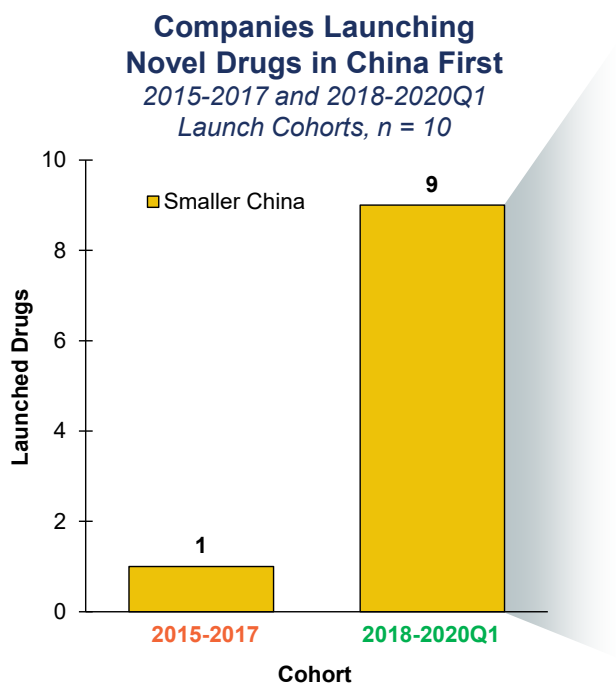
- Nipro's Stemirac (autologous bone marrow mesenchymal stem cells) in 2018
- Shionogi's Xofluza (baloxavir marboxil) in 2018
- Astellas' Xospata (gilteritinib) in 2018
- Roche's Rozlytrek (entrectinib) in 2019

- Novartis' Zolgensma (onasemnogene abeparvovec) in 2020 *(while technically launched first in the US due to a long regulatory review process in Japan, Zolgensma was filed in Japan first and is considered to be an exception from the normal **sakigake** review process and timeline)*

Two of these agents are cell and gene therapies, demonstrating how Japan's focus on regenerative medicines is also showing initial signs of success as an innovative modality in the country.

Novel pipelines of Chinese biotech and biopharma companies have reached the market in growing numbers, with nine novel drug launches in 2018 and 2019

China experienced the most dramatic growth in first launches. Nine novel drugs were launched in China first in 2018 and 2019 compared to only one in the earlier cohort, all by domestic companies (Fig 6). A majority of launches were oncology therapeutics, including three in the blockbuster class of PD-(L)1 inhibitors. However, the drugs cover a variety of other indications such as hepatitis B, HIV/AIDS, psoriasis, and Alzheimer's disease.



Year	Drug Name	Therapeutic Area	Company
2015	Chidamine (Epidaza)	Oncology	微芯生物 CHIPSCREEN
2018	***Danoprevir (Ganovo)***	Infectious Diseases	歌礼 ascletis
	Albuvirtide (Aikening)		Frontier 前沿生物
	Fruquitinib (Elunate)	Oncology	CHI-MED Lilly
	Pyrotinib dimaleate		恒瑞 HENGRUI MEDICINE
2019	Benvitimod (Symbiox)	Autoimmune/ Inflammatory	Beijing Wenfeng Tianji Pharma/ Shenzhen Celestial Pharma
	Sodium oligo-mannurarate	Neurology/CNS	Green Valley 绿谷制药
	Sintilimab (Tyvyt)	Oncology	Innovent Lilly
	Camrelizumab (Iruito)		恒瑞 HENGRUI MEDICINE
	Toripalimab (Tuoyi)		君实生物 TopAlliance

NMPA Priority drug

Figure 6: Companies Launching Drugs in China First

The growth in domestic drug innovation appears to be coming to fruition, supported in part by government initiatives. About half of the recent approvals benefitted from priority reviews by the NMPA. Further, novel agents developed in China have begun approval and marketing efforts internationally, such as Beigene's which launched its BTK inhibitor Brukinsa (zanubrutinib) first in the US in November 2019.

COMMERCIAL DRUG ATTRACTIVENESS IN EUROPE HAS DECLINED IN RECENT YEARS

Novel drug launches by European companies have declined dramatically in recent years

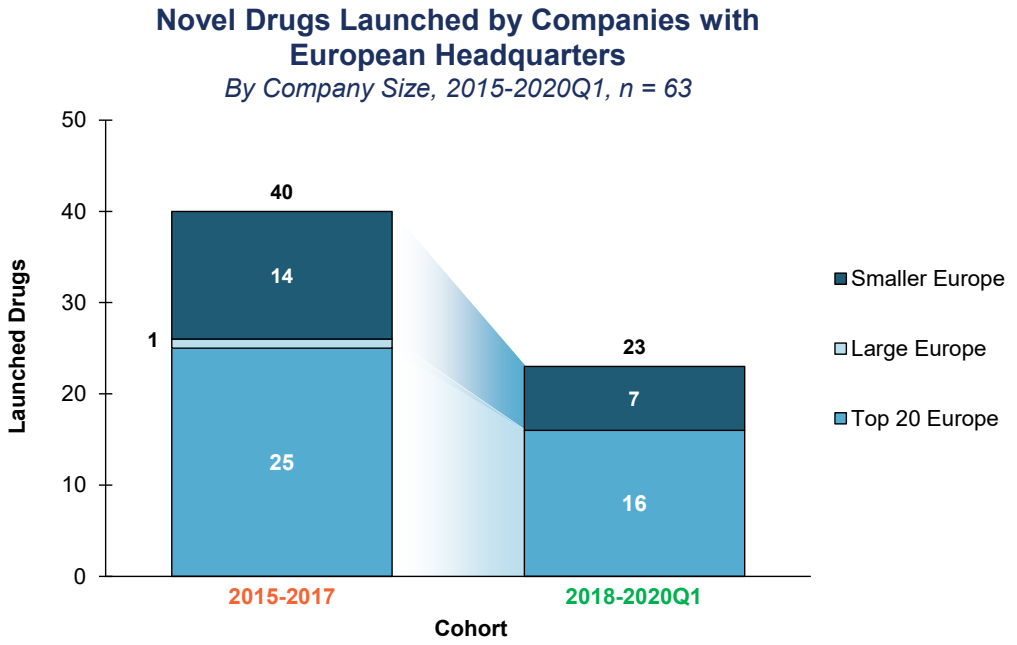


Figure 7: European Domestic Novel Drug Launches

While Japanese and Chinese companies have been launching novel drugs at an accelerating pace, launches by European companies have slowed down. First launches by companies headquarted in Europe dropped by more than 40% in 2018-2020Q1 compared to the previous three years, from multinational companies and smaller regional players alike (Fig 7).

Europe has lost favor amongst companies worldwide as a destination for a drug's first launch

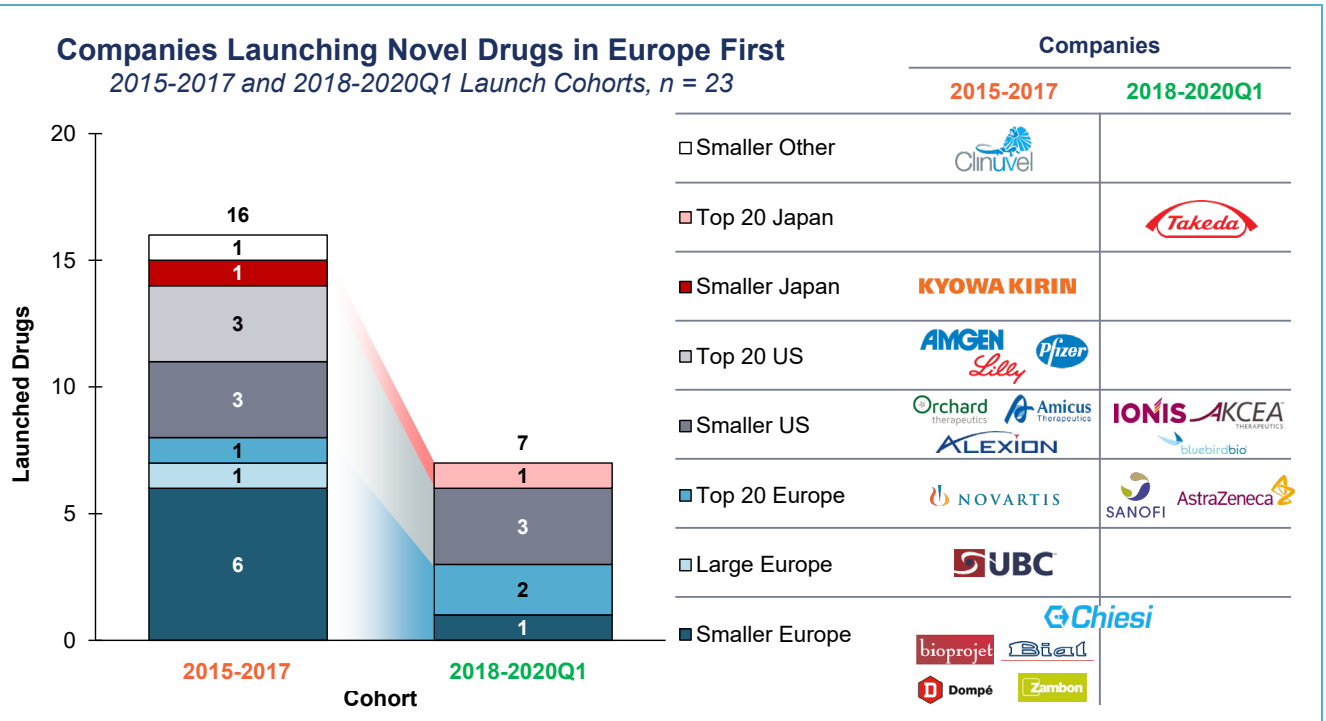


Figure 8: Companies Launching Novel Drugs in Europe First

Additionally, companies around the globe have demonstrated the declining attractiveness of European markets as the choice for initial launch. Between 2015 and 2017, 16 novel drugs were launched first in a European country, but only seven were launched between 2018 and 2020Q1 (Fig 8).

The drugs that launched first in Europe between 2018 and 2021Q1 are indicated for orphan or more specialty indications and nearly all of them were developed by smaller companies that were subsequently acquired (Fig 9).

Drug Name	Company (HQ Region)	Indication	First Launch (Countries)	Notes
Alofisel (Darvadstrocel)	Takeda	Complex perianal fistulas in patients with Crohn's disease	June 2018 (6 European countries)	• Acquired from clinical stage TiGenix (Belgium) • Accelerated EMA review (orphan)
Zynteglo (Betibeglogene autotemcel)	bluebirdbio	Transfusion-dependent ß-thalassemia (TDT)	Jan 2020 (Germany)	• Accelerated EMA review (PRIME and Adaptive Pathway)
Tegsedi (Inotersen)	IONIS AKCEA THERAPEUTICS	Hereditary transthyretin-mediated (hATTR) amyloidosis	Nov 2018 (Germany, US, Canada)	• None
Cablivi (Caplacizumab)	SANOFI	Acquired thrombotic thrombocytopenic purpura	Oct 2018 (Germany)	• Acquired from clinical stage Ablynx (Belgium)
Lamzede (Velmanase alfa)	Chiesi	Alpha-mannosidosis	Dec 2018 (Multiple European countries)	• Acquired from clinical stage Zymenex (Netherlands)
Lokelma (Sodium zirconium cyclosilicate)	AstraZeneca	Hyperkalemia	June 2018 (Nordic countries)	• Acquired from ZS Pharma (US) • Manufacturing delays disrupted intended first launch in US
Waylivra (Volanesorsen)	IONIS AKCEA THERAPEUTICS	Familial chylomicronemia syndrome	Nov 2019 (Germany)	• FDA rejection disrupted intended first launch in US

Figure 9: Novel Drugs Launched First in Europe, 2018-2020Q1

Although this data only describes the dynamics of a drug's country of first launch, it begs the question of whether the current regulatory and market access dynamics are causing novel drug developers to dedicate resources elsewhere. While Europe will remain an important global drug market, only domestic companies that can utilize accelerated review pathways for rare disease treatments are choosing to go-to-marker first in the region.

THE OUTLOOK FOR CONTINUED DRUG INNOVATION IN JAPAN AND CHINA REMAINS STRONG

Biopharma pipelines in Japan and China remain robust, promising continued APAC drug innovation

In addition to Japan and China's growing attractiveness as a geography of first launch and growing domestic company launches, the size of early stage pipelines indicate that these Asia-Pacific countries are well-positioned to sustain their emerging status in drug innovation.

Takeda, Japan's largest biopharma company, emphasizes a strategy to "be courageous and transform our R&D" [Takeda website], which it has been contributing to through internal research and discovery, acquisitions of innovative pipeline agents, and hundreds of strategic partnerships for clinical stage agents.

Similarly, China-based companies have stated their intention to transition from being perceived as generics manufacturers to innovative drug developers ready for global commercialization. Companies such as Beigene, Zai Lab, Innovent, and HUTCHMED have been executing on strategies for global approvals and commercialization of their novel therapeutics. Zai Lab's founder and CEO exemplified this sentiment on a recent earnings call: **"When we founded Zai Lab in 2014, we dedicated ourselves to bringing in first and only-in-class therapies for patients in China and beyond to address significant unmet medical needs"** [Zai Lab Limited, Q4 2020 Earnings Call].

A quick glance at the headquarter location of companies developing novel drugs (defined as new chemical entities in PharmaProjects) also shows that the size of Japan- and China-headquartered company pipelines are growing to compete with the scale of other major geographies (see Fig 10).

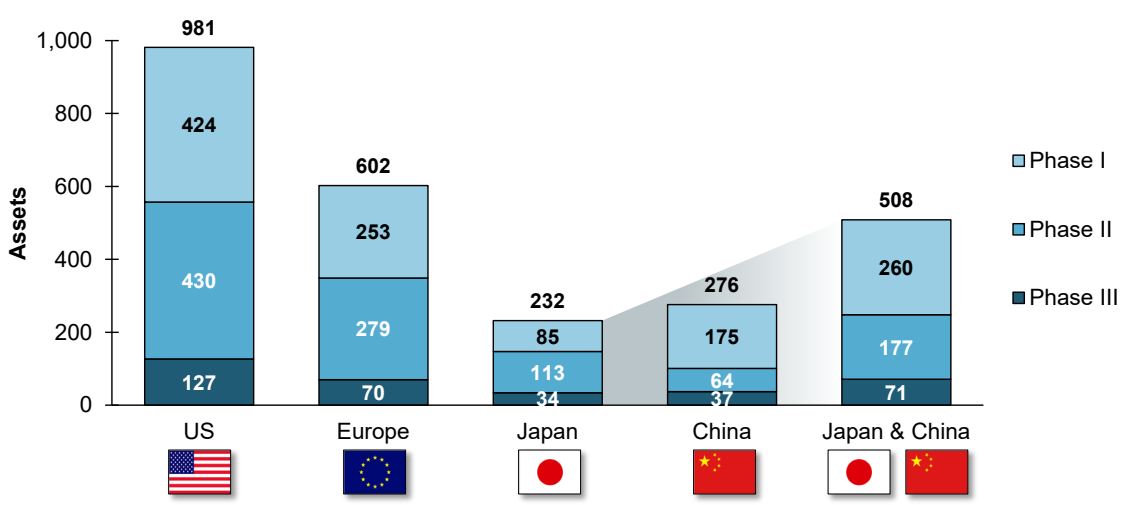


Figure 10: Assets in Development by Company Geography

The overall size of the clinical stage pipeline in Europe remains larger than that of Japan and China, but the similar size of the Phase I pipelines is a strong indication of the growing and sustainable domestic innovation in Asia-Pacific. While this is by no means a robust analysis of regional R&D, it hints Japan and China are indeed invested in drug innovation for the long-run.

An influx of funding in China and Hong Kong will fuel biopharma development in Asia-Pacific

The broader accessibility of global investment and funding toward China-based companies and, notably, recent criteria changes enabling more pre-revenue companies to list on the Hong Kong Exchange (HKEX) has resulted in a recent influx of funding to novel Chinese drug developers. Since the HKEX initiated Chapter 18A in 2018, more than 20 pre-revenue biotechs issued public offerings (see Hong Kong Exchange: Nurturing China's Biotech Valley for more information). Recent listings on the

exchange include companies that have since launched novel drugs in China and the US, including Ascletis Pharma, BeiGene, Innovent Biologics, and Junshi Biosciences.

The growing global appetite to partake in China's innovation shift is also evident through the growth in partnerships and large deals between Western companies and Chinese companies for joint development and ex-US commercialization (Fig 11).

China-based Company	Partner	Partnership Description
BeiGene	AMGEN	• Oct 2019: Amgen and BeiGene enter strategic collaboration to advance oncology pipeline agents and commercialize Amgen oncology agents in China, including $2.7B cash investment by Amgen for 20.5% stake in BeiGene
Innovent 信达生物制药	Roche	• Jun 2020: Roche and Innovent announce a strategic research and development collaboration for hematology-oncology cell therapies and bispecific antibodies, worth up to $1.96B in payments
I-MAB BIOPHARMA	abbvie	• Sep 2020: AbbVie and I-Mab sign a global development and commercialization agreement for the anti-CD47 antibody lemzoparlimab, worth up to $1.74 in milestone payments
基石药业 CSTONE PHARMACEUTICALS	Pfizer	• Sep 2020: Pfizer Investment and CStone enter a collaboration for commercialization of the anti-PD-L1 sugemalimab in China for $200 upfront and $280MM in milestone payments

Figure 11: Select Partnerships and Joint Ventures Between China and Ex-China Biopharmas

CONCLUSION

So where is innovation heading and what is the verdict on the second most attractive market for pharmaceutical innovation? Let's see where the data leads us…

- By country of first launch, Japan and China grew from receiving a similar proportion of global first launches as Europe between 2015 and 2017 to definitively locking in the second most commercially attractive geography position between 2018 and 2020Q1 (Fig 12).
- By domestic drug innovation, companies in Japan and China have accelerated the number of domestic launches whereas those by companies headquartered in Europe have declined (Fig 12).

Further, regulatory and market access dynamics, sentiment regarding novel drug development, and funding support China and Japan's sustained status as global drug innovation leaders.

First Launch Geography

	Europe	Japan and China
2015-2017	13 launches (11% of WW)	16 launches (14% of WW)
2018-2020Q1	6 launches (5% of WW)	28 launches (24% of WW)

Domestic Novel Drug Launches

	Europe	Japan and China
2015-2017	9 launches (8% of WW)	6 drug launches (5% of WW)
2018-2020Q1	4 drug launches (3% of WW)	16 drug launches (14% of WW)

Figure 12: First Launch Country and Domestic Launches of Novel Drugs

The rise in drug innovation has taken a different form in each Asia-Pacific country. Japan has emphasized policies that attract novel drug developers to seek early commercial approval in Japan while cultivating domestic innovation in regenerative medicines. China has primarily invested in local innovation, resulting in a notable increase in novel drug launches by Chinese companies, while starting to open up market access to more global branded drugs.

Here, we only touched briefly on recent trends, but one thing is clear: efforts in Asia-Pacific for drug innovation leadership are starting to pay off and Japan and China's positions in the global drug market are on the rise. It will be an interesting next 10 years as efforts in the region continue bearing fruit and play a part in transforming the global biopharma market.

CONTACT INFORMATION

Are you looking to develop or refine your company's global launch strategy? Or are you interested in learning more about regulatory and market access dynamics in the US, Europe, or Asia-Pacific?

To learn more about Health Advances' expertise and consulting services in global launch strategy and Asia-Pacific (APAC) markets, please contact us at HAAsiaMarkets@healthadvances.comor biopharma@healthadvances.com.

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APPENDIX

Detailed methodology for identifying novel drug launches

Health Advances used Informa's Citeline PharmaProjects database to identify "novel" drugs that were first launched between 2015 and the first quarter of 2021. From a list of 737 agents launched in that time frame, 234 "novel" drugs were identified by removing the following (Fig S1):

- Agents classified as companion diagnostics, imaging agents, biosimilars, reformulations
- Agents deemed to be vaccines or allergy immunotherapies based on Health Advances judgement
- Agents not defined as new active substances via PharmaProjects designation
- Agents with miscategorized launch years (i.e., before 2015 or without a first country of launch reported)

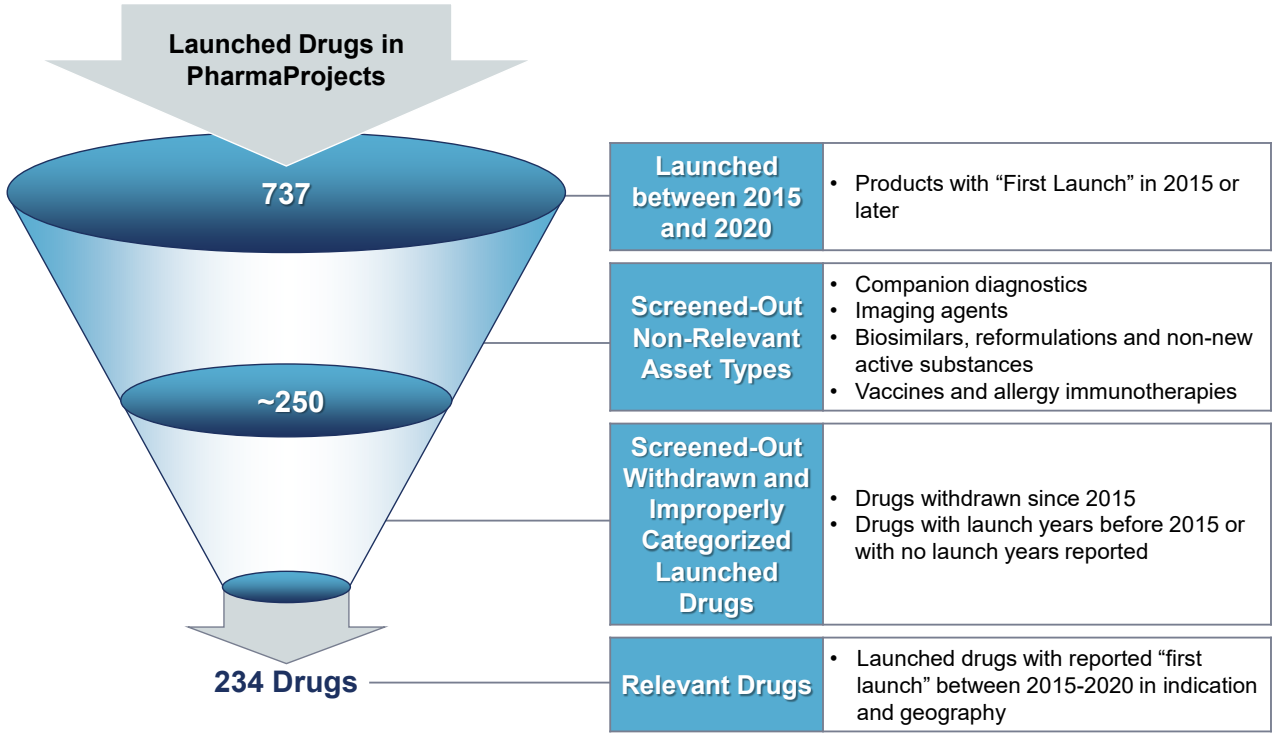

Figure S1: First Launch Country and Domestic Launches of Novel Drugs

Agents were then split into two cohorts based on year of first launch, creating two cohorts of near equal size: 118 agents were launched 2015-2017 and 116 agents were launched 2018-2020Q1 (Fig S2). Health Advances then assigned therapeutic areas based on launched indications. Therapeutic area options were: autoimmune and inflammatory, cardiovascular/metabolic, dermatology, endocrinology, gastroenterology, genitourinary, hematology, infectious diseases, nephrology, neurology/CNS, oncology, ophthalmology, orphan, respiratory, and transplant.

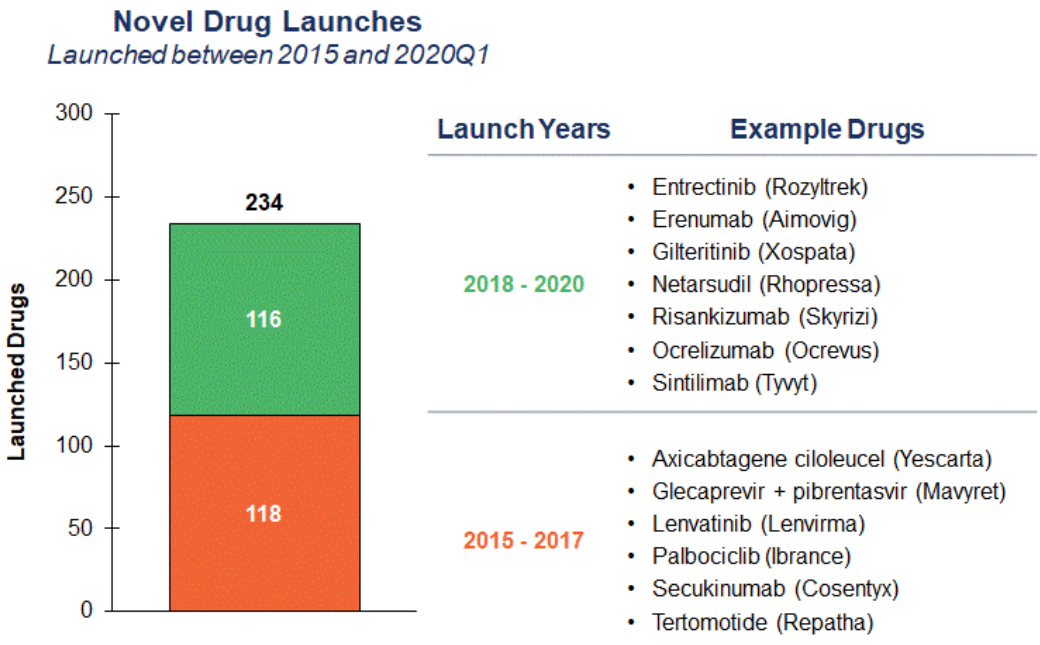

Figure S2: Methodology: Cohort Description