Denise Myshko

The Rise of Biosimilars

The promise of biosimilars is to provide cost-savings, increased patient access, and promote innovation.

The biotechnology market in the United States is about to be altered significantly. In July, Sandoz announced it was the first company to file an application under the biosimilars pathway created by the Biologics Price Competition and Innovation Act. This act, which was part of the Affordable Care Act that was signed into law by President Barack Obama on March 23, 2010, created the regulatory pathway for an abbreviated process for biosimilar products.

Sandoz's application for filgrastim and the reference product, Amgen's Neupogen, are indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with severe neutropenia with fever. Under the brand name Zarzio, the Sandoz biosimilar filgrastim has been marketed in more than 40 countries outside the United States.

Industry analysts expect this to be the first of several applications under the new law, creating competition in the biotechnology market.

Companies are continuing to look at this space because the opportunity is so large, says Vas Narasimhan, M.D., global head development, Novartis Pharmaceuticals, and formerly head of biopharmaceuticals and oncology injectables at Sandoz.

"It is a very sizeable opportunity and if companies do it correctly, the probability of success should be higher than traditional pharmaceutical development and the cost of development should be lower than novel drugs," he says.

High costs of biotech products and access are drivers in the biosimilars market, says Kate Keeping, senior director of biosimilars research at Decision Resources Group.

"The main driver is always going to be the opportunity to save money," she says. "The innovative products that are coming out are expensive, and finding ways for healthcare budgets to afford those new innovative products is high on the agenda for a lot of healthcare systems. In the developing markets, the issue is about market access. Biosimilars will mean more patients can have access to biologic therapies that they wouldn't have had before because of the high cost of the branded product."

Rohit Sood, head of global launch excellence at Campbell Alliance, agrees the market is being driven by patent expirations and increase in healthcare spending, which are forcing governments and payers to look at other treatment options.

"Just like generics in the small molecule

Defining Biosimilar

- **The World Health Organization:** A biotherapeutic that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.
- **The European Medicines Agency:** A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.
- **The FDA:** A biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

> **“If developed correctly, the probability of success for biosimilars should be higher than traditional pharmaceutical development and the cost of development should be lower than novel drugs.”**
>
> **DR. VAS NARASIMHAN**
> Novartis Pharmaceuticals

space, there is a potential for significant uptake, once physicians get more comfortable with biosimilars and patients get used to the idea of being treated with biosimilars rather than the original,” he says.

Sandoz’s application for filgrastim was expected. Sandoz, which is a Novartis Group company, is a pioneer in biosimilars and the global market leader with more than a 50% share of all biosimilars approved in the highly regulated markets of Canada, Europe, Japan, and Australia.

Analysts had anticipated that one of the current players in the biosimilars market to be first with an application in the United States, predicting that early entrants would need access to biologic manufacturing capabilities, experience with clinical trials, experience in regulated markets, and a strong understanding of intellectual property.

Sandoz received the first biosimilar approval in any market: the human growth hormone Omnitrope, which was the first follow-on biologic to be approved in Europe in 2006. In the United States, Omnitrope was approved in May 2006 under the 505(b)(2) pathway. This particular regulatory pathway is a hybrid between the path for new products and generics. It allows for a sponsor to rely, at least in part, on the findings of safety and/or effectiveness for a previously approved drug. It was initially intended to avoid duplication of certain studies and not necessarily a pathway for biosimilars. This regulatory process is generally used when a sponsor is seeking a new indication, has changed a dosage form or active ingredient, or when a product is seeking non-prescription status.

> **“Biosimilars is a significant market, with only a small share needed to achieve worthwhile returns among the top biologic products.”**
>
> **DEEPA DAHAL** / Quintiles

In 2013, Sandoz's biosimilar net sales increased 23% to $420 million. The company's three products include: Omnitrope; Zarzio, a G-CSF for stimulating white blood cell growth during chemotherapy or bone or stem cell transplant; and Binocrit to treat anemia.

The Biosimilars Market

The biosimilars market is expected to be valued at $1.95 billion by 2018, according to MarketsandMarkets. The recombinant glycosylated proteins segment is the largest market and accounted for 40% of the global biosimilars market in 2013 and an estimated $314.2 million; it is expected to grow at a CAGR of 17.5% from 2013 to 2018. The biggest factor behind the growth of this segment is the increasing demand for second-wave biosimilar insulin and interferon products for the treatment of diabetes and infectious disorders. Of all the segments in the product category, the monoclonal antibodies sector is the fastest-growing at an estimated CAGR of more than 40% from 2013 to 2018.

Europe dominates the global biosimilars market accounting for about a 40% share in 2013. The factors driving the European market are its well-defined regulatory guidelines; numerous pipeline products; and more than 15 biologics going off-patent in the coming years.

Biosimilars, however, require a high investment. The savings between biosimilars and biologics are not as substantial as first anticipated, with the cost of biosimilars expected to be about 20% to 30% lower than that of branded biologic therapies, say analysts at GlobalData.

Oncology is the largest and fastest-growing segment and accounts for a 25% share of the global biosimilars market, according to the MarketsandMarkets report. This is attributed to the increasing prevalence of cancer, as well as the rise in the aging population.

Raymond Huml, DVM, executive director of biosimilars strategic drug development and planning, global biosimilars unit, at Quintiles, says trends driving the market include: low R&D productivity; waves of originator biologic patent expiries; significant market potential; and regulatory pathways that are becoming defined, making it easier for companies to pursue development; global regulatory disparity, which makes it easier for sponsors to conduct smaller trials and reach the market more quickly in some countries; access to capital and chemistry, manufacturing and controls (CMC), and clinical trial expertise by partnering; mandated use of biosimilar products by governments and payers in some countries to cut health care costs; and the desire for patients to get affordable copies of expensive biologics.

> **"Trends driving the biosimilar market include low R&D productivity; waves of originator biologic patent expiries; significant market potential; and regulatory pathways that are becoming defined, making it easier for companies to pursue development."**
>
> **DR. RAYMOND HUML** / Quintiles

This is a significant market, with only a small share needed to achieve worthwhile returns among the top biologic products, says Deepa Dahal, consultant, Quintiles.

"The market opportunity can be further increased if biosimilars lead to the treatment of new patients, those who are not currently treated by biologics at all," she says.

Ms. Dahal says the companies best suited for success in the biosimilars market are those with existing biotech expertise, as well as those that are willing and able to invest in robust, high-quality biologic manufacturing plants and processes and in strong commercialization efforts, such as physician and payer education and patient support.

But there are many significant barriers to entry, including the high levels of investment required for biosimilar drug development programs, depending on the country and numbers of patients required for clinical trials.

"It also takes sophisticated CMC expertise and access to capital," Dr. Huml says. "Players will need a high tolerance for risk — clinical, legal, regulatory, commercial, etc. — and many smaller companies wishing to cash in on this market may fail because they do not have the marketing muscle to compete against the giants."

George Scott, VP of bioanalytical services at inVentiv Health Clinical, says there is an underappreciation for the resource needs from both a capital and technical level to take a molecule and turn it into a feasible asset.

"Companies that may be more in tune with the small molecule generic business will be shocked about the clinical development needs for a biologic product vs. a small molecule," he says.

Mr. Sood agrees, adding that while technology has improved and, while not easy, companies can now develop cell lines that are similar to an originator.

"Today, it is possible to manufacture with a high level of quality, whereas a few years ago, there were greater technical challenges," he says. "What it takes beyond manufacturing to make money in the biosimilar market is something that very few companies have thought about. For entrepreneurial companies the focus seems to be more on manufacturing a product that a large biopharma company may hopefully be interested in in-licensing or co-promoting. The larger companies, such as Pfizer and Amgen, which have publically stated they are going after biosimilars, understand the biologics space and what it takes to compete."

The manufacturing process is another challenge. Dr. Huml says even small changes can produce untoward safety signals.

"Many of the larger companies today are a product of acquisitions and mergers," he says. "With many different manufacturing plants handling different parts of the process, there is the potential for variance that is unacceptable to the regulatory agencies. Those companies that have successfully manufactured products in Europe and are looking to market in the United States, for example, will have an advantage over companies that have not marketed their products anywhere."

Regulatory Issues

In May 2014, the Food and Drug Administration released a draft guidance for how the agency will evaluate biosimilarity as well as to help sponsors design clinical pharmacology studies. Specifically, the guidance discusses some of the concepts related to clinical pharmacology testing, approaches for developing the appropriate clinical pharmacology database, and modeling and simulation for designing clinical trials.

The guidance provides four outcomes of assessment. A product could be deemed similar, not similar, highly similar, or similar with "fingerprint-like similarities." Regulatory officials say highly similar with fingerprint-like

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>
> **KATE KEEPING** / Decision Resources Group

Physician Perspectives on Biosimilars

Physicians' perspectives on the topic of biosimilars vary by specialty, and some are not convinced they are clinically similar enough to start using them right after launch, says Kate Keeping, senior director of biosimilars research at Decision Resources Group.

"Oncologists, particularly those in Europe, are already using biosimilars to a certain extent and they have very different opinions about biosimilars in comparison with other specialists, such as gastroenterologists," she says. "There is a wide variety of opinions, which is driven by the patients they treat, whether they are children or adults, whether they are treating them for a few months or over a lifetime, whether they are using products that are very complex, such as large monoclonal antibodies or recombinant proteins that essentially human-made proteins. All of these factors have an influence on physicians using biosimilars."

Ms. Keeping says the marketing message for a biosimilar needs to focus on the product delivering similar patient outcomes as the branded product and not solely on costs.

"The concept of a biosimilar drug is still relatively new, so marketers need to promote the message about the drug; it shouldn't be just about costs," she says. "It's about showing the data are similar and the outcomes can be similar as well."

Ms. Keeping says the message needs to be tailored depending on the clinical or payer audience being targeted.

"For physicians, messages need to focus on clinical data, but if you are speaking with payers focusing more on the cost savings is likely to be more influential in that setting," she says.

similarity means the proposed biosimilar product meets the statutory standard for biosimilarity based, in part, on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.

A fingerprint-like analysis would further quantify the similarity or differences between the two products using a meaningful algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods.

The results of these fingerprint-like analyses permit a very high level of confidence in the analytical similarity of the proposed biosimilar and the reference product, and it would be appropriate for the sponsor to use a more targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity.

FDA officials say in terms of clinical pharmacology studies, the assessment of a proposed biosimilar product is designed to address uncertainty regarding any clinically meaningful difference between the proposed biosimilar product and the reference product. Potential differences that will be evaluated are pharmacokinetics (measures of drug exposure) and, when appropriate, pharmacodynamics (measures of drug effect at a given drug exposure).

Ms. Keeping says while the guidance provided no surprises, the inclusion of four categories of similarity was new.

"Regulators haven't specified how these are going to be used, but they are in the process of publishing more guidelines this year," she says. "One guidance of interest to the industry is on interchangeability. Another is the agency's position on how biosimilars are going to be named, but that might be in the labeling document."

Andrew Bourgoin, senior pharmaceutical analyst at Thomson Reuters, says the fingerprint similarity gives the industry an indication of what the agency would likely consider for a biosimilar to be interchangeable with the reference product.

"This guidance isn't specific to interchangeable products, but since interchangeable products are going to be very significant in the large molecule biologics market down the road, seeing this description within this guidance document gives the industry an idea of what to expect moving forward," he says.

Agency officials say they expect to issue a guidance sometime this year pertaining to considerations in demonstrating interchangeability to a reference product.

CDER continues to meet with sponsors interested in developing biosimilar products. As of May 31, 2014, CDER had received 67 requests for an initial meeting to discuss biosimilar development programs for 14 different reference products and held 57 initial meetings with sponsors. CDER is actively engaging with sponsors, including holding development-phase meetings and providing written advice for ongoing development programs for proposed biosimilar products.

To date, CDER has received 23 INDs for biosimilar development programs, and additional development programs are proceeding under a pre-IND. As of May 31, 43 programs are in the biosimilar product development program.

Mr. Sood says the May guidance, along with other notifications, provides a way to calibrate expectations.

"In tandem with the technical document that was released in 2012 and other documents on formal meetings between FDA and biosimilar sponsors, these help to normalize thinking around biosimilars," he says. "One of the things we try to get across is that the proposal for the product's development will change. It would be unusual to start a development program today and for it not to change. The regulatory agency has put in place a very healthy scientific and formal proposal for communication with companies. That will be very helpful in conjunction with the technical guidance."

Dr. Huml says this guidance is just the start of a series of guidances that, together, will be more impactful.

"The May guidance is not as prescriptive as the European guidelines are for certain biosimilars," he says. "Europe has been approving biosimilars for eight years and has acquired 300 million days of safety and efficacy data. The United States has yet to approve a biosimilar via the 351(k) route, the route designated in 2010 as the path to biosimilar approval."

Dr. Narasimhan says one of the keys to success is working with regulators to design clinical trials that meet the endpoints, but he notes that even Sandoz, with all of its experience in the biosimilar space, has had to approach development as a learning process.

"In each area, it has been a different experience for us," he says. "In supportive-care oncology and supportive-care renal products, we've been able to enroll these studies very quickly. In oncology, there was a learning curve in terms of enrollment; but we are now past that curve." PV

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Partnering for Success

To be successful in the biosimilars market, partnering with various experts is key.

Most companies are not in a position to succeed in the biosimilar market unaided, experts say.

"Biosimilar manufacturers are recognizing that there are limitations, and they are partnering with very interesting types of companies to access geographic reach, technical capabilities, development expertise, manufacturing expertise, or marketing capability," says Rohit Sood, head of global launch excellence at Campbell Alliance. "There are some interesting partnerships evolving in this area and it's almost a requirement for success. Very few companies will be able to be successful in the biosimilar space on their own."

Andrew Bourgoin, senior pharmaceutical analyst at Thomson Reuters, points out that the biosimilar market is one in which few of the companies involved are fully integrated vertically to have all of the capabilities to succeed.

"We've seen quite a few partnerships to fill competency gaps, for example in manufacturing," he says. "Biomanufacturing requires capabilities that are different from small molecule manufacturing. Other partners are providing opportunities into other markets. Other partnering opportunities fill gaps in experience and expertise in more than just the generics space. We've seen some partnerships between biotech and more traditional generic players, where both sides are hoping to leverage capabilities and competencies to succeed in the market."

GlobalData researchers say there are more than 100 deals involving companies focused on the development of biosimilars that have been completed over the past seven years, with a total value in excess of $10.7 billion.

Deepa Dahal, a consultant at Quintiles, says generic companies have CMC expertise, but may not have clinical trial or marketing expertise and may benefit from partnering to share risk, obtain capital, and acquire expertise and resources to advance biosimilars.

"Partnerships can enable companies to complement one another's strengths in areas such as manufacturing, marketing and market access," she says.

Mr. Bourgoin says there are four basic competencies that are required to succeed in this market: manufacturing capability, market experience, clinical experience, and IP or patent challenge experience.

"We've had 30 years of experience with generic small molecules, but the biosimilar market has been around for eight years," he says. "With the complexity of manufacturing, it makes sense there is still uncertainty." PV

Approved Biosimilars in Europe

Reference brand	Reference molecule	Biosimilar company	Biosimilar name
Eprex	epoetin alfa	Medice Arzneimittel Putter	Abseamed
Gonal-F	follitropin alfa	Finox Biotech	Bemfola
Eprex	epoetin alfa	Sandoz (Novartis)	Binocrit
Neupogen	filgrastim	CT Arzneimittel (Teva)	Biograstim
Eprex/Erypo	epoetin alfa	Hexal Biotech (Novartis)	Epoetin alfa Hexal
Neupogen	filgrastim	Hexal Biotech (Novatos)	Filgrastim Hexal
Neupogen	filgrastim	Apotex/Intas	Grastofil
Remicade	infliximab	Hospira	Inflectra
Neupogen	filgrastim	Hospira	Nivestim
Genotropin	somatropin	Sandoz (Novartis)	Omnitrope
Gonal-F	follitropin alfa	Teva	Ovaleap
Neupogen	filgrastim	Ratiopharm (Teva)	Ratiograstim
Remicade	infliximab	Celltrion	Remsima
Eprex	epoetin alfa	Hospira	Retacrit
Eprex	epoetin alfa	STADA	Silapo
Neupogen	filgrastim	Teva	TevaGrastim
Neupogen	filgrastim	Sandoz (Novartis)	Zarzio/EP2006

Source: Decision Resources Group

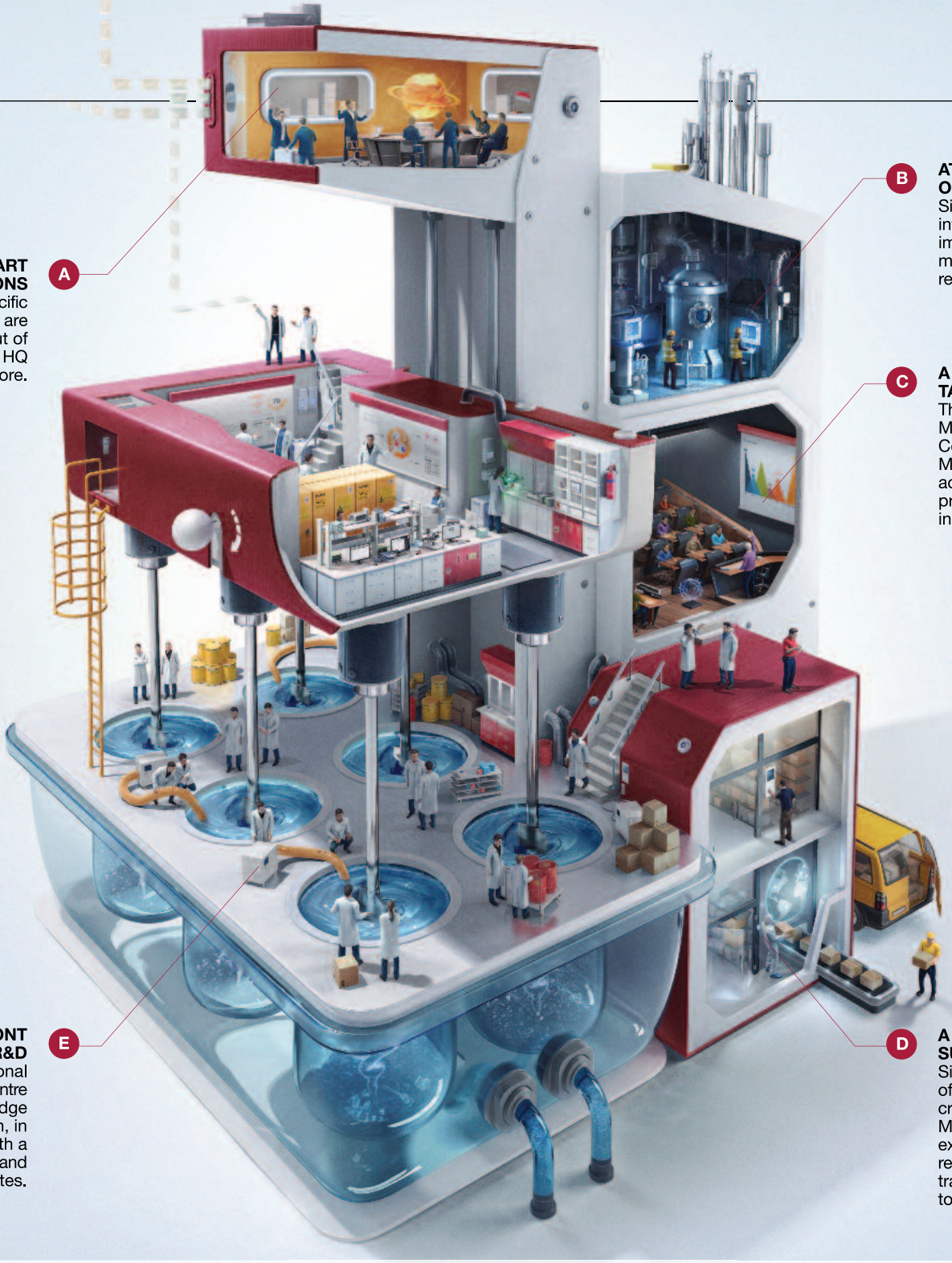
Biosimilars and the FDA

The FDA's latest draft guidance on biosimilars, issued in May 2014, discusses three key concepts:

- **Exposure-response assessment:** Well-designed clinical studies in a biosimilar development program evaluate the similarities and differences between a proposed biosimilar product and a reference product. Evaluating a person's response when exposed to a biological product helps determine safety, purity and potency of any biological product, and may highlight potential clinically meaningful differences between two products.
- **Evaluation of residual uncertainty:** The FDA will consider the data and information submitted as a whole, using a risk-based approach, while evaluating an application that supports a demonstration of biosimilarity. When evaluating clinical pharmacology, the FDA looks closely at pharmacokinetic, pharmacodynamics and safety data obtained in conjunction with the clinical pharmacology studies.
- **Assumptions about analytical quality and similarity:** Sponsors should conduct extensive and robust comparative structural and functional studies to evaluate whether the proposed biosimilar product and the reference product are highly similar. A meaningful assessment depends on, among other things, the capabilities of available state-of-the-art analytical tools to assess the product.

MSD WITH SINGAPORE:

Finding the right mix for success



A AT THE HEART OF OPERATIONS
MSD's Asia Pacific operations are managed out of their Regional HQ in Singapore.

B AT THE HELM OF PRODUCTION
Singapore has world-class infrastructure, and an impressive track record meeting worldwide regulatory standards.

C A SKILLED TALENT POOL
The Biopharmaceutical Manufacturers' Advisory Council (BMAC) lets MSD work with tertiary academic bodies on programs to meet industry needs.

D A GLOBAL SUPPLY CHAIN
Singapore's network of logistics partners is critically important to MSD. It enables the export of products requiring cold chain transport and storage to the rest of the world.

E AT THE FOREFRONT OF R&D
MSD's Translational Medicine Research Centre focuses on cutting-edge medical research, in partnership with a network of research and academic institutes.