

Developing Innovative Medicines for Patients Around the World with a Global Research Network

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Boehringer
Ingelheim



Together with Dr. Scheld, Representative Director, Chairman and President, who kindly took our interview.

“We really want to contribute to fields with unmet medical needs where patients are still waiting for effective treatments,” says Dr. Jan Stefan Scheld, Representative Director, Chairman, and President of Nippon Boehringer Ingelheim Co., Ltd, a pharmaceutical company that develops drugs for a wide range of conditions, from those with large patient populations, including diabetes, to rare diseases, including psoriasis. The company works diligently across a wide range of disease fields and in all stages of clinical development with activities ranging from the early stages of research through to the final delivery of pharmaceuticals into the hands of physicians treating patients.

Boehringer Ingelheim is renowned as the only unlisted company among the 20 global pharmaceutical companies with the largest sales revenue. Boehringer Ingelheim is headquartered in Germany but operates globally with Nippon Boehringer Ingelheim forming a crucial part of the group. While they have traditionally focused on respiratory, cardiovascular, and metabolic areas, the company has recently expanded into other areas including the treatment of skin and inflammatory diseases, mental health, and oncology. I had an opportunity to visit Nippon Boehringer Ingelheim headquarters in Tokyo’s Osaki district and talk with Dr. Scheld and Dr. Koichi Wada, Executive Officer and Head of Kobe Pharma Research Institute, to learn more about their work.

A rare, unlisted pharmaceutical company

Boehringer Ingelheim is an unlisted pharmaceutical company. The non-public nature of the company is a core part of its identity, setting the company apart from other industry players. Over the decades, the founder's family has remained in control of the firm.

The company was founded in 1885, when Albert Boehringer established a chemical factory in the small German village of Ingelheim to manufacture lactic acid. Over time, even as the company has expanded its business globally to cater to a diverse range of medical needs, Boehringer Ingelheim has remained family-owned and stably run.

As a family-owned company, Boehringer Ingelheim maintains consistent management principles grounded in long-term perspectives. In many cases, public companies must focus on shareholder return, which means they must produce reports each quarter that meet shareholders' expectations. While other pharmaceutical companies have grown rapidly by going public, Boehringer Ingelheim has chosen to remain unlisted and committed to long-term, consistent drug development.

Dr. Scheld explains that, as a family-owned company, Boehringer Ingelheim is determined to contribute to transforming patients' lives for generations by building trust and addressing

medical needs with a long-term horizon.

As Boehringer Ingelheim attempts to address the demands of society, it is the importance that the company places on trust that allows its researchers to take full responsibility for long-term research and development, starting from the earliest stages of drug discovery. In addition, by working together in partnership with experts and delegating authority to employees where appropriate, Boehringer Ingelheim puts in place an environment in which every individual can make maximum use of their talents as the company works to see a project through to a conclusion.

Trust is the foundation of healthy debate among researchers. They trust each other to engage in frank debate, asking questions such as "Are you positive that you are right?" rather than unquestioningly accepting others' conclusions. Frank debate ensures that the company's science is grounded in solid evidence; the business can then be built on that science. Dr. Scheld, who became the Chairman and President of Nippon Boehringer Ingelheim this autumn, spoke to the importance of this process, noting that "we can still do more in Japan to build a culture of robust challenges and encouraging each other".

Dr. Scheld also stressed Boehringer Ingelheim's ability to develop drugs in line with long-term research and development strategies, starting from the moment during the early drug discovery stages when a potential compound is found through to the delivery of the final product to the patients who require it.





Delivering drugs from Japan to patients around the world

For the German-based global company, Japan is a crucially important location, not only because it is the company's second-largest market after the USA, but also as it is a strategic center of the company's global operations, hosting both research and production facilities.

With such an important position in the company, Nippon Boehringer Ingelheim is expected to make a significant, intellectual contribution. Through the production of new discoveries and ideas, and the exchange of talents between Japan and the rest of the world, the company aims to foster individuals who make a significant global contribution to the company's operations.

The Kobe Pharma Research Institute, or KPRI, plays an important role in this process. As Boehringer Ingelheim's only laboratory-equipped R&D center in Asia, it is responsible for global research and development from non-clinical research to CMC^[1]. The center's activities include (i) research into pharmacokinetics and formulation design, (ii) serving a bridging function that provides Boehringer Ingelheim with access to external innovation through partnerships with third parties such as universities and start-ups, and (iii) work to obtain regulatory approval from the Japanese pharmaceutical authorities.

Their pharmacokinetic research investigates the functions of drug transporters, which are proteins that facilitate the transportation of drugs, either by allowing drugs to enter targeted cells (uptake transporters) or by removing them from cells (efflux transporters) to prevent in-cell accumulation. This research provides insight into how drugs are distributed within the body as well as how drugs interact with other drugs, information which sheds light on the drugs' therapeutic effects, appropriate dosage, and safety. KPRI is involved in research on the interactions

between drug transporter and candidate compounds throughout Boehringer Ingelheim's global network.

Their work to develop drug formulations deals with the design of solid preparations for oral administration. In other words, they research and develop the design of the formulations used to ensure that drugs can be provided both effectively and safely. Designing oral formulations is a critical field of research work, as over half of all standard prescription pharmaceuticals are taken orally. Through analytical research, they evaluate and optimize factors including drug absorption and stability, which leads to the development of more efficient and easier-to-take drugs. Within Boehringer Ingelheim's global pipeline for low-molecular-weight drugs, KPRI is responsible for around 40% of the research projects into drug formulation design.

KPRI's work on pharmacokinetics and the development of formulations has been driven by leveraging advanced knowledge and technology in Japan. Boehringer Ingelheim recognizes the value of Japan's cumulative track record of research in these fields, which, according to Dr. Wada, "has not been exploited fully on a global scale". Based on this observation, the company has absorbed and further developed in-house the high-level knowledge and technical skills that academic institutions and other parties possess in the field of pharmacokinetics and formulation development.

However, Boehringer Ingelheim is now involved not only in the downstream research and development area which gives 'shape' to newly developed drugs, the company is also involved in the upstream processes of searching for new drug candidates. KPRI's Business Development and Licensing Group is involved from the early stages in the incorporation of innovative seeds from outside the company as well as in the exploration of new technology in the therapeutic areas in which Boehringer Ingelheim currently offers products and maintains a focus. Additionally, Boehringer Ingelheim's Research Beyond Borders team is exploring outside the company's traditional core therapeutic areas, partnering with startups and universities to explore drug discovery seeds and new technologies.

With Boehringer Ingelheim harnessing its global research network to develop drugs for global markets, Nippon Boehringer Ingelheim is working to leverage Japanese expertise and technology in pursuit of that goal. Dr. Scheld spoke passionately about the topic saying, “My dream is for innovation in Japan to result in a product that we can provide to patients around the world. I truly hope that dream will come true.”

Addressing further unmet medical needs

Throughout its extensive history, Boehringer Ingelheim has developed a range of medications for respiratory, cardiovascular, and metabolic diseases, significantly advancing their knowledge and technology in these areas. Presently, they provide drugs for diabetes, a metabolic disease, to many patients, which form the company’s core business. What areas will the company focus on in the future?

“Our fundamental stance is to contribute to areas with significant unmet medical needs,” says Dr. Scheld. Nippon Boehringer Ingelheim focuses its business on the following six areas: cardiovascular diseases, metabolic diseases, oncology, respiratory diseases, skin and inflammatory diseases, and psychiatric and central nervous system diseases.

Among these fields, the company is particularly focused on expanding into areas related to circulatory and metabolic diseases. Currently, one of the company’s core products is a diabetes drug, and the company has extensive expertise in this field. The company is, therefore, exploring ways to apply its knowledge to other diseases. For example, some forms of chronic heart failure and chronic kidney disease often occur in diabetic patients. For such diabetes-related diseases, Boehringer Ingelheim expects to use its expertise in diabetes to conduct research and development for these conditions, as it sees significant potential for progress in these areas.

The company is currently researching and developing pulmonary fibrosis treatments. Patients with pulmonary fibrosis, a refractory disease, experience the progressive transition of healthy lung tissue into hard fibrous tissue. Lost pulmonary elasticity leads to symptoms including breathing difficulty. Boehringer Ingelheim considers the unmet medical needs surrounding pulmonary fibrosis to be a key treatment area, and in 2014, the company launched an effective pulmonary fibrosis treatment (launched in Japan in 2015).

The company is also now focusing on immunology and oncology. As an example of its entry into immunology, Dr. Scheld and Dr. Wada spoke about the development of a drug for pustular psoriasis, a rare skin disease in which white blisters of noninfectious pus (which consists of white blood cells) appear surrounded by red skin with a sudden onset of fever. Boehringer Ingelheim realized a drug to treat this disease by a “miracle-like” finding, according to Dr. Scheld. Studies of the inflammatory cytokine IL-36 (a bioactive substance that regulates intercellular

What BI is looking for in prospective interns

Dr. Scheld

We would love to have people with proven excellence in and passion for their field. We are also looking for people who have broader experience and knowledge, including those who have lived abroad, with the ability to talk about common sense, and everyday topics, in addition to their specialist area of research.



Dr. Wada

During your internship, we aim to provide you with the actual research environment and themes as much as possible. We would like you to enjoy interacting and conducting research with your team of various specialties. In addition, since research is often done by a global team, we would like you to experience a global research environment while you are in Japan.



[Photo provided by Nippon Boehringer Ingelheim]



29th October is “World Psoriasis Day”. Dr. Scheld wears a psoriasis awareness T-shirt. Boehringer Ingelheim is actively promoting the social understanding and support for psoriasis. [Photo provided by Nippon Boehringer Ingelheim]

signaling) and an investigation of which diseases are induced by the IL-36 pathway showed that neutrophil abnormalities are a leading cause. Similarly, pustular psoriasis is also a disease caused by neutrophil abnormalities. Consequently, the development of a drug targeting IL-36 was initiated, anticipating its effectiveness. After collaborating with Japanese experts for the clinical development in Japan, they successfully obtained approval for the drug, an anti-IL-36R monoclonal antibody, in 2022.

Crafting solutions for rare diseases requires a totally different business approach. Optimized research and development methods are needed to adapt to the smaller numbers of patients. For example, it is more important to consult with clinical experts who have specialized experience. It is also important to work with the Pharmaceuticals and Medical Devices Agency, which scrutinizes and authorizes newly developed medicines, to arrange feasible clinical trials while maintaining rigor, as large-scale trials can be difficult to conduct. Besides administering drugs, raising awareness and understanding of these diseases in society is crucial for improving patient care. Nippon Boehringer Ingelheim partners with the Japanese Society for Psoriasis Research to offer an educational program to medical professionals ^[2]. The company is also committed to the ‘Illuminate Tomorrow’ initiative, which involves incorporating the experiences of individuals with pustular psoriasis to find solutions through the cooperation of INSPIRE JAPAN WPD and to educate the broader public ^[3]. They strive to deliver solutions for rare diseases, mobilizing the whole company and the entire society.

Boehringer Ingelheim also seeks to contribute to the field of oncology. As the industry as a whole is increasingly focused on oncology, Boehringer Ingelheim is concentrating on two primary

areas: immunotherapy and cancer cell-targeted treatments ^[4]. Immunotherapy involves the development of platforms such as T Cell Engager (TCE), oncolytic viruses, and cancer vaccines that can potentially turn cold tumors into hot ones. The company is also working on cancer cell targeted treatments and believes a key element in this field is intracellular growth factors. Many cancer cells effectively use growth factors to proliferate. Therefore, Boehringer Ingelheim researchers are focusing their research on how to intervene in the activities of growth factors. By pursuing these approaches, Boehringer Ingelheim is creating new possibilities in cancer therapy.

Nippon Boehringer Ingelheim has teamed up with the National Cancer Center, the base of cancer research and care in Japan, to jointly develop individual candidate drugs starting at the early phases. Boehringer Ingelheim values the National Cancer Center as a key strategic partner in their global research and development network. Their partnership is extensive and strong, covering all aspects of oncology research and development, from first-in-human trials (the clinical trial phase when a drug is administered to humans for the first time) to sharing ideas beyond individual projects. Dr. Scheld states, “This is an amazing example of how Japanese expertise and capabilities can be used in medicine worldwide.”

By making use of knowledge developed in Japan for its operations around the world, Boehringer Ingelheim seeks to contribute towards unmet medical needs through business strategies that build upon foundations established by the company in the key disease areas it has tackled over the years while also expanding into new disease areas.

What Boehringer Ingelheim values

According to Dr. Wada, the corporate culture at the company is focused on every employee's commitment to delivering drugs, and through teamwork and competition, each individual develops personally and the company grows. They also value seeing science with hope, which consistently evolves, and they aim to utilize its progress to effectively create new and innovative medicine.

Dr. Scheld chose 'trust', 'respect', 'empathy', and 'passion' as words to describe Boehringer Ingelheim. Employees have the same passion that "truly wants to contribute to the fields in which patients are suffering." Respecting colleagues, being committed extensively to the search for effective compounds and to delivering drugs to the people who need them, working to prove worthy of the trust of partners, governments, society, and patients, and above all, being passionate about "Transforming lives for generations" is the essence of Boehringer Ingelheim.

Column: Author's perspective on the future of Boehringer Ingelheim

The healthcare industry is evolving around collecting and analyzing big data. In the search for effective compounds, the pharmaceutical industry now commonly uses 'combinatorial chemistry', which efficiently generates large numbers of compounds, and 'high-throughput screening,' whereby a robot automatically evaluates a library of compounds to identify those effective against a particular disease^[5].

Meanwhile in the upstream of healthcare, transformations based on data science are being made in testing and diagnostics. For example, an Israeli start-up is creating technology to identify disease-triggering phenotype combinations by collecting and analyzing phenotyping data on a large scale and comparing the phenotypes of healthy individuals and patients. In Japan, albeit a latecomer, momentum is gaining for using medical big data called 'real-world data', such as medical fee statements and health check-up results, for healthcare business and 'health management'. In this 'century of data' there is tremendous potential to bring new breakthroughs in healthcare by effectively utilizing medical big data.

In this changing scenario, the author proposes that Boehringer Ingelheim could contribute further to personalized healthcare and early intervention by integrating its drug discovery





**Representative Director, Chairman and President
Dr. Jan Stefan Scheld**

efforts with the development of testing and diagnostic technologies. By collaborating with companies and research institutions that develop testing and diagnostic technologies, the company would pool extensive clinical data from various medical stages to create comprehensive datasets for specific diseases. This would then enable early and proactive treatment, including tailored medication, based on the individual patient's disease progression and profiles.

In the field of diabetes, one of Boehringer Ingelheim's core domains, there is a quest for new ways of treating the disease that take into account the unique profiles of each individual patient. Instead of relying solely on the traditional classifications of type 1 and type 2 diabetes, scientists are now looking at phenotypic data analysis to better understand the differences between patients [6]. The author suggests that Boehringer Ingelheim share their extensive knowledge and data in the fields of diabetes, rare diseases, and oncology with companies and research institutions involved in developing testing and diagnostic technology. Specifically, the author suggests sharing their knowledge and data with 'clinical core research hospitals' that possess a wealth of clinical data for phenotypic profiling. By gaining a deeper understanding of diseases and implementing an integrated and comprehensive approach to developing the therapeutic process, including testing, diagnosis, and drugs, they could potentially create more effective and less burdensome drugs and dosing methods.

Acknowledgement

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**Executive Officer and Head of the KPRI
Dr. Koichi Wada**

individuals at Nippon Boehringer Ingelheim who contributed significantly to our visit, including those who explained the business, took photographs, arranged interviews, reviewed the manuscript. Thank you.

(Interviewed on 2nd August, 2023)

【Notes】

[1] CMC stands for Chemistry, Manufacturing, and Control. It covers the research and development of the Chemistry of active ingredients and drug formulations, as well as Manufacturing processes, and quality Control.

[2] Nippon Boehringer Ingelheim (2023) "日本乾癬学会・日本ベーリンガーインゲルハイムが共同開発 指定難病膿疱性乾癬 (GPP) を対象とした初の学会提携教育プログラム『PIONEERS®GPP』を発表 (The Japanese Society for Psoriasis Research and Nippon Boehringer Ingelheim announce the joint development of 'PIONEERS® GPP', the first educational program partnered with an academic society targeting pustular psoriasis, a designated intractable disease)"
https://www.boehringer-ingelheim.com/jp/stories/20230825-1?fbclid=IwAR1-FTunRIEaFulg2DXXTdDCH2m8hClpfBfQvb0uiTkVeBLp_KTdjJXZNY (Accessed: 8th December 2023)

[3] Nippon Boehringer Ingelheim (2022) "日本ベーリンガーインゲルハイム、膿疱性乾癬をはじめとした稀少疾患患者さんの未来を照らす啓発プロジェクト『Illuminate Tomorrow』始動 (Nippon Boehringer Ingelheim launches 'Illuminate Tomorrow', an awareness-raising project to lighten up the future of patients with pustular psoriasis and other rare diseases)"

[4] Boehringer Ingelheim. (2023) Why cancer care is personal for us
<https://www.boehringer-ingelheim.com/human-health/cancer/why-cancer-care-personal-us> (Accessed: 6th September 2023)

[5] Pisano, Gary. (2006) *Science Business: The promise, the reality, and the future of biotech*, Harvard Business School Press.

[6] Deutsch, Aaron J., Emma Ahlqvist, and Miriam S. Udler. (2022) Phenotypic and genetic classification of diabetes. *Diabetologia*, 65, 1758–1769.

What is it like to work at KPRI?

Nippon Boehringer Ingelheim believes that each employee is essential to the company. That is why we provide support to ensure that all of our people can make the best of their abilities and potential.

For example, Science Café, a free-form discussion forum, was launched from the voices of young researchers in 2020. It has been running successfully for four years, and the network is now expanding to include not only laboratory staff but also members from other departments.

Through presentations and discussions on various themes, including the latest topics in their respective specialist areas, attendees at Science Café can explore topics they may not encounter in the course of their regular work. As such, the café serves as a vital forum for communication.

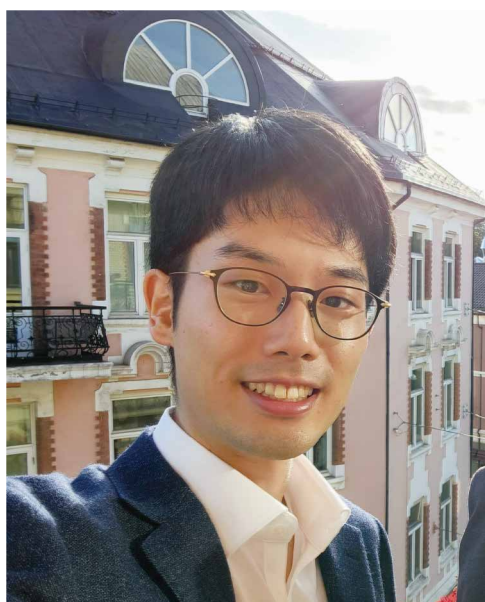
Based on the workplace culture that welcomes the opinions of each individual, we are striving to energize our company by proposing, sharing, and realizing new ideas, thereby enhancing our competitive edge in research and development.

Additionally, we have various systems in place for supporting the career development of our employees, including offering opportunities to study for a doctorate and, for those keen on working abroad, overseas work placements lasting a few months.

Nippon Boehringer Ingelheim is committed to providing a work environment in which every individual employee can develop their talents and reach their full potential.

Company overview

- Corporate name : Nippon Boehringer Ingelheim Co., Ltd.
- Founded : 30th June, 1961
- Capital : JPY 7,200 million
- Representative : Representative Director, Chairman and President Dr. Jan Stefan Scheld
- Employees : About 1,670 (as of January 2023)
- HQ location : ThinkPark Tower 2-1-1 Osaki, Shinagawa-ku, Tokyo, Japan
- Line of business: Research, development, import, manufacturing and marketing of medicines



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Message from C-ENGINE

As the 4th installment of the "Exploring C-ENGINE Members" series to introduces the attractiveness of our members, we had the privilege of collaborating with Nippon Boehringer Ingelheim to interview Dr. Scheld, who newly became Representative Director, Chairman and President in September 2023, and Dr. Wada, executive officer and head of KPRI. We explored their passion in the business, the significance of having research and development centers in Japan, and various other perspectives. We encourage everyone to participate in the research internships to experience its culture where each employee challenges themselves directly, respects one another, and earnestly contributes to society!

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