Kirin Holdings Co., Ltd.

Kirin Holdings engages in alcohol beverages, non-alcohol beverages, and pharmaceuticals and bio-chemicals business.

- The Pharmaceuticals and Bio-chemicals business includes:
    - Kyowa Hakko Kirin Co. Ltd.
    - ProStrakan Group plc → now known as Kyowa Kirin (since April 18, 2016)
    - Kyowa Hakko Bio Co., Ltd.
    - Kyowa Kirin Frontier
    -

Pharmaceutical businesses they have outside of Japan:

- Kirin-Amgen, Inc. (U.S.)
- Gemini Science, Inc. (U.S.)
- Hematech Inc. (U.S.)
- Jeil-Kirin Pharmaceutical, Inc. (South Korea)
- Kirin Pharmaceuticals Company, Ltd. (Taiwan)
- Kirin Pharmaceuticals (Asia) Company, Ltd. (Hong Kong)
- Kirin Kunpeng Bio-Pharmaceutical Company, Ltd. (China)

Kyowa Hakko Kirin Co., Ltd. – a pharmaceutical and biotechnology that centers on antibody engineering
https://www.kyowakirin.com

- Conducts development, manufacturing and sales of drugs and therapeutic antibodies based on bio-technology
- Focus on areas of oncology, nephrology, central nervous system, and immunology
- They offer products related to amino acids and nucleic acids in the fields of pharmaceuticals, medicine, and healthcare
- General company details:
    - Is among the 40 largest in the world by revenue
    - Founded in 1949
    - Number of employees: Over 7000
    - Annual revenue: 346 billion yen
    - Operating profit: 58 billion yen
    - Currently they have 4 antibody drugs released and 4 in pipeline
    - Chairman: Nobuo Hanai
    - President and CEO: Masashi Miyamoto
    - Offices in Japan, U.S., Uk, China, Korea
- Financial results: https://ir.kyowakirin.com/en/library/earnings.html?_ga=2.218859153.960152318.1565187855-903805719.1565187855#19q2
- The company developed a method to make afucosylated monoclonal antibodies using a CHO cell line in which FUT8 has been knocked out → the company calls this its "POTELLIGENT" platform

    - The company gained marketing approval in Japan in April 2012 for a monoclonal antibody drug called mogamulizumab which was developed using this platform
    - Mogamulizumab is used for the treatment of relapsed or refractory adult T-cell leukemia/lymphoma and relapsed or refractory cutaneous T cell lymphoma (approved in 2014)
- They focus on technology-driven drug discovery based on 4 key modalities:
    - Next Generation Therapeutic Antibodies
        - The fundamental technologies of Kyowa Kirin in the production of therapeutic antibodies are characterized by POTELLIGENT and human-antibody producing mice technologies
        - They are engaged in research and development of next generation therapeutic antibodies
    - New Types of Small Molecule Drugs
        - Their approach to small molecule drug discovery involves rational drug design → structure-based drug design ranging from the structural analysis of disease-associated biomolecules (therapeutic target) to the design of small molecules
    - Nucleic Acid Drugs
        - Kyowa Hakko is actively working on the development of nucleic acid drugs which are attracting attention as new therapy
    - Regenerative Medicine
- They currently have numerous drug candidates in the works
    - Ex. KHK4827 to treat Psoriasis

Main products:

- ESPO/NESP – an erythropoiesis stimulating agent (ESA) with longer-lasting effect than conventional erythropoietin drugs
    - Effective for improving renal anemia
- REGPARA – a new class of agent for the treatment of secondary hyperparathyroidism
    - Acts on parathyroid calcium receptor directly and suppresses parathyroid hormone secretion, while lowering serum calcium and phosphorus levels
- GRAN/Peglasta/Neulasta – a human colony-stimulating factor (G-CSF) produced by genetic recombination technology
    - Works to selectively increase the count and functional efficacy of a type of white blood cell called neurotrophil
- Romiplate/Nplate – a genetically recombinant protein
    - Stimulates platelete production via stimulation of the thrombopoietin receptors
- Crysvita – a recombinant fully human monoclonal lgG1 antibody against the phosphaturic hormone fibroblast growth factor 23
    - By blocking excess FGF23 in patients, this drug intends to increase phosphate reabsorption in the kidney and increase the production of vitamin D

    - This enhances intestinal absorption of phosphate and calcium in patients with X linked hypophosphatemia
- Poteligeo – a humanized monoclonal antibody that targets CC chemokine receptor 4 (CCR4) which is frequently expressed in leukemic cells

Kyowa Kirin International plc – a subsidiary of Kyowa Hakko Kirin Co. Ltd.
https://www.kyowakirin.com

- In 2011, Kyowa Hakko Kirin Co. Ltd bought Scottish drug firm ProStrakan Group Plc for $474.6 million
    - This allowed Kirin to establish European and U.S. sales platforms as well as a Suite of specialist prescription products
- Engages in administration and management of subsidiaries under
- Acquired Archimedes Pharma from the Novo Nordisk Foundation for $394 million on July 11, 2014

Kyowa Hakko Bio Co., Ltd. – subsidiary of Kyowa Hakko Kirin Co. Ltd.
http://www.kyowahakko-bio.co.jp/english/

- Established in 2008
- Capital of 10,000 million yen and revenue of 81.1 billion yen
- President: Takeshi Minakata
- Goal: to be a biochemical innovator that provides clients with products and services to fulfill their healthcare needs, using their deep knowledge of fermentation and synthesis
- Offices in Tokyo, New York, Germany, Italy, Singapore, India, and multiple in China
- They are engaged in the manufacturing and sales of pharmaceutical and industrial raw materials and healthcare products, among others
    - Ex of raw materials: amino acids, peptides, oligosaccharides, nucleic acids
    - Supplies high quality materials such as amino acids, nucleic acids and dipeptides which are essential for pharmaceuticals, dietary supplements/foods, and cosmetics
    - Provide high quality bulk API (Active Pharmaceutical Ingredient) to pharmaceutical companies around the world
    - They also actively develop new products in collaboration with pharmaceutical companies to expand their base of operations
- The company sets out to respond to the global demand for high-value amino acids due in part to rising levels of healthcare and call for generic drugs
- In 1956, Kyowa Hakko Kirin became the first company in the world to succeed in the industrial production of amino acids using fermentation methods
    - Since then, Kyowa Hakko Bio has released a wide range of amino acids and has been a global leader in the field
- Kyowa Hakko Bio has discovered an enzyme with dipeptide synthesizing activity → this enzyme reacts with a variety amino acids to yield multifarious dipeptides

Kyowa Kirin Frontier Co., Ltd.

- Established in January 2017 as part of the "Creating Shared Value management based on unique business structure" within the Contribution to Health and Well-being of People, which was one of the core strategies set forth by Kyowa Kirin
- They work toward obtaining approval to manufacture and market authorized version of NESP
- Estimated capital in 2017: 100 million yen

News

Kyowa Kirin Buys Back Tivozanib Non-Oncology Rights from AVEO Oncology – Aug 1, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190801_01.html

- Kyowa Kirin and AVEO Oncology announced that they have amended their license agreement to allow Kyowa Kirin to buy back the non-oncology rights of tivozanib in AVEO territories, excluding the rights which are currently sublicensed to EUSA Pharma
    - Tivozanib is an oral, vascular endothelial growth factors tyrosine kinase inhibitor discovered by Kyowa Kirin → approved for the treatment of adult patients with advanced renal cell carcinoma
- Kyowa Kirin is obligated to an upfront payment of $25 million to AVEO and up to $391 million in potential milestone payments upon successful achievement of certain objectives in non-oncology indications of tivozanib
    - Kyowa is also obligated to make tiered royalty payments on the net sales of these indications
    - Agreement also waives AVEO's obligation to make an $18 million milestone payment upon AVEO gaining the U.S. marketing approval

Kirin Announces Launch of Darbepoetin Alfa Injection syringe in Japan – July 30, 2019
https://www.marketscreener.com/KYOWA-HAKKO-KIRIN-CO-LTD-6491339/news/Kyowa-Hakko-Kirin-Notice-Regarding-Change-of-Trade-Name-Partial-Amendments-to-the-Articles-of-Inc-27064755/

- Announced on July 30th, 2019 that its wholly owned subsidiary Kyowa Kirin Frontier Co., Ltd. will launch Darbepoetin Alfa Injection Syringe in Japan on August 5
    - Darbepoetin Alfa Injection Syringe was approved in Japan on Aug 15, 2018 and is an authorized version of NESP
    - This will help patients with Chronic Kidney Disease (CKD)

Kyowa Hakko Kirin Receives Partial Approval of Romiplate for Aplastic Anemia in Japan – June 18, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190618_01.html

- Romiplate (AMG531) is a treatment of aplastic anemia (AA) in patients who have had an inadequate response to conventional therapy
- It was launched for the treatment of idiopathic thrombocytopenic purpura (ITP) and has contributed to many ITP patients since April 2011

Kyowa Hakko Kirin Announces Top-Line Results of Phase 3 Study of Brodalumab (KHK4827) in Patients with Axial Spondylarthritis – June 17, 2019

- The company announced positive results of a 16-week efficacy and safety analysis of the phase 3 study of Brodalumab in patients with axial spondylarthritis and non-radiographic axial spondylarthritis
- The study showed that more patients who were given Brodalumab showed an improvement of equal to or above 40% and an absolute improvement of above or equal to 2 units compared to the control group ay week 16
    - There were also no apparent differences in safety between the 2 groups
- This showed that Brodalumab was well tolerated in 16 weeks and effective for the treatment of axSpA
- Study was conducted in Japan, South Korea, and Taiwan

Kyowa Hakko Kirin Launches Mirai Port – June 13, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190613_01.html

- The company launched its new Sustainable Development Goals (SDGs) website, Mirai Port to raise awareness of SDGs and the company's actions

Kyowa Hakko Kirin Submits the Partial Change Approval Application of KHK7580 (evocalet) in Japan – April 24, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190424_01.html

- The company announced that they submitted a supplemental application of KHK7580 (evocalcet) for the treatment of hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after it, to the Ministry of Health, Labor and Welfare in Japan
- This application was based on the results of the phase 3 study that evaluated the efficacy of KHK7580
- KHK7580 was also granted Orphan Drug Designation for the treatment of this group of patients by the Ministry of Health, Labor and Welfare on March 4, 2019

Kyowa Kirin Announces FDA Acceptance of Istradefylline (KW-6002) – April 4, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/pdf/e20190404_01.pdf

- Kyowa Hakko Kirin announced that the U.S. FDA has accepted froe review the resubmitted New Drug Application for istradefylline (KW-6002) – an investigational selective adenosine for use as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "off" episodes

Kyowa Hakko Kirin Enters New Development and Commercialisation Agreements with AstraZeneca for All Benralizumab Indications beyond COPD and Asthma in Asia – March 25, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190325_01.html

- Kyowa Kirin announced that they have entered a new agreement with AstraZeneca, granting AstraZeneca exclusive rights to benralizumab (brand name Fasenra) for all additional indications in Asia, inclusive of Japan

    - AstraZeneca now has global rights to benralizumab for all current and future indications
- Under the agreement, AstraZeneca will pay Kyowa Hakko Kirin up-front and subsequent payments for regulatory and commercial milestones
- AstraZeneca will now be responsible for development, sales, and marketing of benralizumab for all indications in 14 Asian countries and regions
- Benralizumab is now approved as an add-on maintenance treatment in severe, eosinophilic asthma in the US, EU, Japan, and several other jurisdictions

Kyowa Kirin Asia Pacific Announces Establishment of Subsidiary in Australia – March 18, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190318_01.html

- Kyowa Kirin Asian Pacific Pte. Ltd (a wholly owned subsidiary of Kyowa Hakko Kirin CO., Ltd.) announced that it has established an Australian subsidiary, named Kyowa Kirin Australia Pty Ltd.
    - Which this expansion they aim to launch Kyowa Hakko Kirin's global strategic products into Australia

Ultragenyx and Kyowa Kirin Announce Positive 64-Week Results for Crysvita (burosumab) from Phase 3 Study in Children with K-linked Hypophosphatemia – Feb 15, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/pdf/e20190215_01.pdf

- Results showed that Crysvita was superior to conventional therapy for all key efficacy endpoints
- Crysvita is an antibody that blocks fibroblast growth factor 23 – a hormone that causes an excess of phosphate urinary excretion and suppresses active vitamin D production by the kidney

Kyowa Hakko Kirin Initiated Phase 2 Clinical Study of Tenapanor (KHK7791) for Hyperphosphatemia Patients on Hemodialysis in Japan – Feb 6, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190206_01.html

- Phased 2 clinical study was initiated in Japan for tenapanor – a small molecule compound licensed from Ardelyx, Inc.
    - Tenepanor is an oral, minimally systemic NHE3 inhibitor with a unique mechanism that is different from the current phosphate binder therapy
- Phase 2 sets out to evaluate serum phosphorus in hyperphosphatemia patients on Hemodialysis who switch from phosphate binders to KHK7791 in Japan
    - The study will evaluate the efficacy and safety of a switch from phosphate binders to KHK7791
- Kyowa Hakko Kirin also plans to initiate 2 additional phase 2 clinical trials for KHK7791 0
    - A monotherapy dose-response study and a combination therapy with KHK7791 and phosphate binders
- Kyowa Hakko Kirin signed a license agreement with Ardelyx for the exclusive rights to develop and commercialize tenapanor in cardiorenal disease in Japan on November 28, 2017

Hisamitsu Pharmaceutical and Kyowa Hakko Kirin sign Commercialization Agreement for HP-3000 (a Potential New Transdermal Patch for Parkinson's Disease in Japan) – Feb 5, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190205_02.html

- The two companies entered an agreement granting Kyowa Hakko exclusive rights to commercialize HP-3000
    - Kyowa Hakko will be responsible for commercializing the product after Hisamitsu Pharmaceutical receives a manufacturing and marketing approval for the product in Japan
- The product is a systematic transdermal Parkinson's disease treatment patch developed by Hisamitsu Pharmaceutical's TDDS technologies
- Hisamitsu Pharm will receive an upfront payment and milestone payments based on the regulatory approval and sales amount

Kyowa Hakko Kirin Announces Changes in Global Management Structure – Feb 5, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/pdf/e20190205_05.pdf

- The company announced changes to its global management structure to "One Kyowa Kirin" effective April 1, 2019
    - Under this new structure, Kyowa Kirin Group will be organized both by region and function
- Kyowa Kirin USA Holdings Inc. will be responsible for North America's market
- Kyowa Kirin International PLC will in the future, be responsible for the Europe, Middle East, and Africa market
- A Global Product Management Office will be newly established directly under the control of president of Kyowa Hakko Kirin to unify the management of Kyowa Kirin Group's global strategic products
    - Tomohiro Sudo, currently VP of Kyowa Kirin International PLC was appointed as the new Head of Global Product Management Office

Kyowa Hakko Kirin Submits Application for Approval of Burosumab in Japan – January 7, 2019
https://www.kyowakirin.com/media_center/news_releases/2019/e20190107_01.html

- The company filed an application for manufacturing and marketing approval with Japan's Ministry of Health, Labor and Welfare for burosumab to treat FGF23-related hypophosphatemic rickets and osteomalacia
    - Burosumab is antibody that was discovered by Kyowa Kirin and was developed to treat FGF23-related hypophosphatemic disease such as x-linked Hypophosphatemia and tumor-induced osteomalacia/epidermal nevus Syndrome
    - Burosumab is designed to bind to and thereby inhibit the biological activity of FGF23 → by doing so, it increases phosphate reabsorption from the kidney and increases the production of vitamin D, which enhances intestinal absorption of phosphate and calcium
- Burosumab received orphan drug designation in Japan

- The company expects to receive feedback regarding manufacturing and marketing approval for burosumab around September 2019
- Kyowa Hakko Kirin, Kyowa Kirin International PLC, and Ultragenyx Pharmaceutical Inc. has been collaborating in the development and commercialization of burosumab globally

Ultragenyx and Kyowa Kirin Announce Health Canada Approval of Crysvita (burosumab injection) for the Treatment of X-linked Hypophosphatemia in Adults and Chidlren – Dec 6, 2018
https://www.kyowakirin.com/media_center/news_releases/2018/e20181206_01.html

- The product is expected to be available for prescription to Canadian patients in early 2019
- This offers patients with XLH the first treatment option that targets the underlying cause of their rare disease
- Crysvita is now approved in the US, Europe, and Canada
- Burosumab is the first treatment to address the fundamental problem in this disease – renal phosphate wasting

Kyowa Kiririn Announces POTELIGEO Receives Marketing Authorisation in Europe – November 26, 2018
https://www.kyowakirin.com/media_center/news_releases/2018/e20181126_01.html

- POTELIGEO will be the first biologic agent targeting chemokine receptor 4 (CCR4) to be available for patients with mycosis fungoides or Sezary Syndrome n Europe
    - Mycosis fungoides (MF) and Sezary Syndrome (SS) are the 2 most common subtypes of cutaneous T-cell lymphoma
- Kyowa Kirin plans to launch POTELIGEO in various markets in Europe from 2019
    - Kyowa Kirin International PLC will be responsible for commercialising POTELIGEO in Europe

GSK and Kyowa Hakko Kirin sign strategic commercialisation deal in Japan for daprodustat, a potential new oral treatment for anaemia associated with chronic kidney disease – Nov 22, 2019
https://www.kyowakirin.com/media_center/news_releases/2018/e20181122_01.html

- The two companies announced a strategic collaboration for the future commercialisation of daprodustat in Japan
    - Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor currently in phase 3 development by GSK for the treatment of anaemia associated with chronic kidney disease
- GSK will be responsible for the completion of the ongoing phase 3 clinical programme and regulatory submissions for marketing authorisation in Japan
- Distribution of daprodustat will be conducted by Kyowa Hakko Kirin
- Positive results from two phase 3 studies in dialysis dependent Japanese patients were recently announced

MEI Pharma and Kyowa Hakko Kirin Announce License Agreement to Develop and Commercialize ME-401 in Japan – Nov 5, 2018
https://www.kyowakirin.com/media_center/news_releases/2018/e20181105_01.html

- This agreement granted Kyowa Hakko Kirin exclusive rights to develop and commercialize ME-401 in Japan
    - MEI is a treatment for patients with B-cell malignancies

Kyowa Hakko Kirin Announces a Phase 1 Clinical Study of its IDO Inhibitor in Solid Tumor 0 Nov 2, 2018
https://www.kyowakirin.com/media_center/news_releases/2018/e20181102_01.html

- Kyowa Hakko Kirin entered a collaboration agreement with Merck kGaA, Darmstadt, Germany and Pfizer to initiate a Phase 1 clinical study of Kyowa Hakko Kirin's novel IDO inhibitor, KHK2455, in combination with avelumab (a human anti-PD-L1 antibody for solid tumors)
- Kyowa Hakko will initiate a Phase 1 clinical study in the US
- Avelumab has received accelerated approval by the FDA for the treatment of patients with metastatic Merkel cell carcinoma (MCC) and previously treated patients with locally advanced or metastatic urothelial carcinoma (mUC) and is under further evaluation across a range of tumor types
    - However, Avelumab is under clinical investigation for treatment of solid malignancies and has not been demonstrated to be safe and effective for these uses

Mylan and Fujifilm Kyowa Kirin Biologics Receive European Marketing Authorization for Hulio – Sep 20, 2018

- MylaN.V. and Fujifilm Kyowa Kirin Biologics Co. Ltd announced that the European Commission has granted marketing authorization for Hulio → a biosimilar to AbbVIe's Humira (the world's best-selling biologic medication)
    - This follows the adoption of a positive opinion by the Committee for Medicinal Products for Human Use
    - This approval applies to all 23 EU countries and the European Economic Area member states
- Mylan plans to launch Hulio across various markets in Europe on or after Oct 16
- Hulio is indicated for the same indications of Humira
    - Ex. rheumatoid arthritis, psoriasis, Crohn's disease

Kyowa Hakko Kirin Announces Results of Early Phase 2 Trial of KW-6356 for Parkinson's Disease – Aug 20, 2018
https://www.kyowakirin.com/media_center/news_releases/2018/e20180820_01.html

- The study showed that KW-6356 monotherapy is well tolerated and effective in the treatment of motor symptoms in early PD patients
- The company plans to initiate late phase 2 clinical trial in Japan by the end of 2018
- KW-6356 is a selective antagonist of adenosine A2A receptors developed by Kyowa Hakko Kirin

FDA Approves of Poteligeo for the Treatment of Mycosis Gunfoides and Sezary Syndrome – Aug 9, 2018
https://www.kyowakirin.com/media_center/news_releases/2018/e20180809_01.html

- FDA granted approval for Poteligeo for the treatment of adult patients with relapsed or refractory mycosis fungoides or Sezary syndrome after at least 1 prior systemic therapy
- Using the proprietary POTELLIGENT technology, the amount of fucose in the sugar chain structure of Poteligeo is reduced → this enhances the antibody dependent cellular cytotoxicity
- FDA granted Poteligeo Breakthrough Therapy Designation for the treatment of MF and SS in adult patients and evaluated Poteligeo with Priority Review
    - This is reserved for drugs that treat a serious condition and if approved, would provide a significant improvement in treatment safety or effectiveness
- Kyowa Kirin International PLC and Kyowa Hakko Kirin Co. will be responsible for commercializing Poteligeo in the U.S.

http://globalmarketnews24.com/32991/global-asparaginase-market-2019-kyowa-hakko-kirin-alize-pharma-jinan-welcome-biochemical-pharmaceutical/

- Kyowa Hakko Kirin was listed as one of the leading Asparaginase Industry players in the Global Asparaginase Market 2018 Research Report

https://pledgetimes.com/2019/08/09/animal-based-food-amino-acid-market-swot-analysis-and-surge-from-2019-2025-ajinomoto-inc-japan-kyowa-hakko-kirin-group-japan-sigma-aldrich-co-llc-u-s/

- Kyowa Hakko Kirin was listed as one of the top prominent players the Global Animal-based Food Amino Acid Market Research Report

https://industrynewsfeed.com/24285/global-drugs-for-non-small-cell-lung-cancer-market-2019-kyowa-hakko-kirin-hikma-pharmaceuticals-curis/

- Kyowa Hakko Kirin is recognized as one of the top manufacturers for the Non-Small Cell Lung Cancer Market