Cannabinoid manufacturing

Innovative approaches to the production of cannabinoids

Edison themes

27 April 2022

The cannabis market is growing fast. According to BDSA, cannabis sales grew by 50% and 41% in 2020 and 2021 respectively, which brought 2021 sales to US$31bn. The demand for isolated cannabinoids is also growing, with Grand View Research estimating the cannabinoid market was worth US$4.5bn in 2020 and forecasting a CAGR of 20.4% until 2027, which would take the market size to US$16.4bn. The demand is driven by the wellness and pharmaceutical industries. A variety of manufacturing methods are being developed that have the potential to produce industrial-scale, low-cost, high-quality cannabinoids. Manufacturing innovations in extraction, chemical synthesis, biosynthesis and biotransformation are all attracting significant investment.

Historical and current restrictions

The use of cannabis for medical and recreational use remained illegal across the globe for decades. It was only in the 2000s that broad amendments to laws permitting usage began. In 2012, Colorado and Washington were the first states to legalise the use of recreational cannabis. Since then, a further 16 states have legalised the use of recreational cannabis and, altogether, 38 states have legalised medical cannabis. In other parts of the world, legalisation around medical and recreational cannabis is mixed. Notably in Germany, the use of medical cannabis has been legal since 2016 and it is expected that recreational use will become legal in the near future.[1]

Legalisation is opening the cannabinoid market

Across the globe, the legalization of medical and recreational cannabis is opening new markets and opportunities. The most well-known of these is the cultivation of cannabis flowers. There is also a growing demand for the isolated chemical compounds found inside cannabis plants, cannabinoids. The most notable of these is the non-psychoactive compound cannabidiol (CBD), which is widely used within the wellness industry. There is also growing interest in rare cannabinoids that are only found in very low quantities within cannabis plants. R&D efforts are also looking at novel cannabinoids, which are analogues of naturally occurring cannabinoids that remain structurally similar to the original molecules. Both rare and novel cannabinoids are of particular interest to the pharmaceutical industry, as they could have new medical applications.

Cannabis and cannabinoids market size

According to BDSA, a leading cannabis market research firm, global cannabis sales grew 50% y-o-y in 2020, and then an additional 41% in 2021, bringing global sales to US$31bn. BDSA forecasts global cannabis sales to grow to US$62bn in 2026. The cannabinoid market is also growing. According to a report by Grand View Research, the US cannabinoid market size was US$4.5bn in 2020 and is forecast to reach US$16.4bn in 2027. To capitalize on this projected growth, many companies are developing innovative manufacturing processes to bring high-demand, high-quality cannabinoid products to the market.

Edison themes

As one of the largest issuer-sponsored research firms, we are known for our bottom-up work on individual stocks. However, our thinking does not stop at the company level. Through our regular dialogue with management teams and investors, we consider the broad themes related to the companies we follow. Edison themes aims to identify the big issues likely to shape company strategy and portfolios in the years ahead.

Companies mentioned in this report (Edison clients in bold)

Amyris
BayMedica
BioHarvest Sciences
CB Therapeutics
Creo
Cronos Group
Demetrix
Genomatica
Ginkgo Bioworks
GW Pharmaceuticals
InMed Pharmaceuticals
Jazz Pharmaceuticals
LAVVAN
Lygos
PharmaCann
Pfizer
Purisys
Recipharm
Willow Biosciences

Analyst

Dr Elliott Lumb +44 (020) 3077 5700

healthcare@edisongroup.com

Classes of cannabinoids

Cannabinoids are a group of chemical substances that interact with the body's cannabinoid receptors. They can be produced naturally by cannabis plants, or in a lab through biosynthesis or chemical synthesis. The cannabis plant is the most well-known source of these chemical substances; it is known to produce over 100 different cannabinoids. The two most prevalent cannabinoids in the plant are tetrahydrocannabinol (THC) and cannabidiol (CBD).

THC and CBD

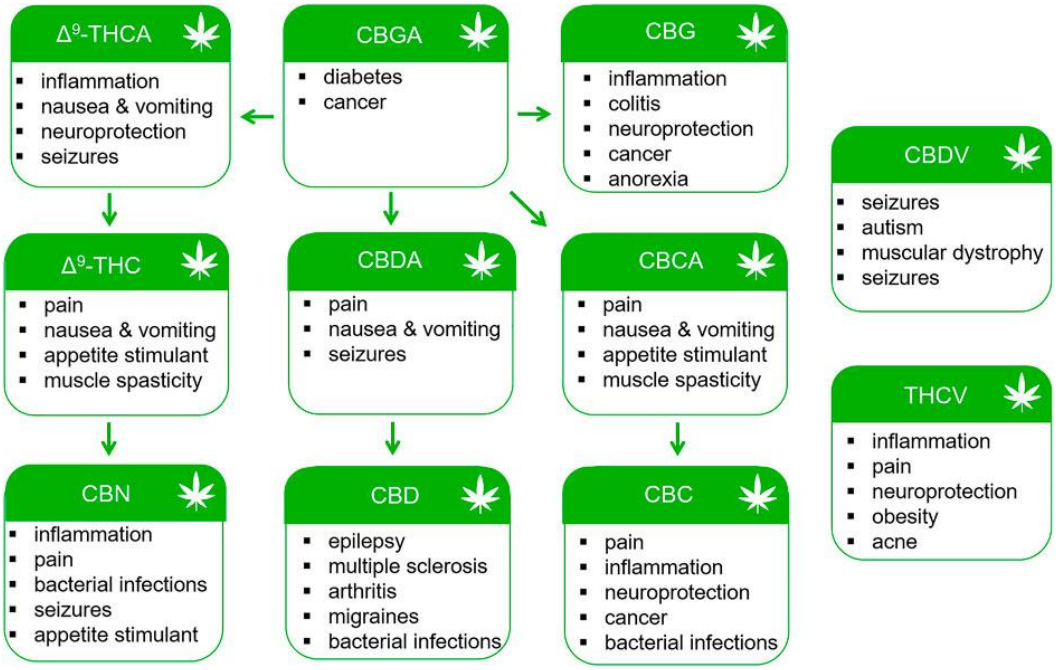
THC is the substance responsible for the psychoactive effects of cannabis, which makes a person 'high'. It is the main active ingredient in medical cannabis. Aside from in Canada and 18 US states, the recreational sale of THC is broadly illegal. CBD does not induce psychoactive effects and is federally legal across the United States (when derived from hemp) and legal across much of Europe. In 2015, the FDA reduced regulatory restrictions on CBD, which allowed researchers to conduct clinical trials. This was followed by the Farm Bill in 2018, which legalised hemp, and consequently, CBD, which naturally occurs in hemp. GW Pharmaceuticals developed the first CBD prescription drug, Epidiolex, which was approved by the FDA in June 2018 to treat seizures caused by several conditions. Within the pharmaceutical and wellness industries, there is significant interest in CBD to treat conditions such as anxiety, insomnia and chronic pain.

Rare and novel cannabinoids

Rare, or minor, cannabinoids are generally defined as naturally occurring cannabinoids other than THC or CBD. Typically, these chemicals will make up 0.1% to 10% of the cannabinoids that can be extracted from a cannabis plant. Due to their limited quantity, it can be difficult to isolate them. However, it is thought that each of these could have interesting pharmaceutical properties. Examples of rare cannabinoids include cannabichromene (CBC), cannabidiolic acid (CBDA), cannabidivarin (CBDV), cannabinol (CBN) and tetrahydrocannabivarin (THCV). While previously considered rare, cannabigerol (CBG) can now be obtained more readily than previously, through the use of genetically modified hemp plants. In terms of the varied potential uses of rare (or minor) cannabinoids, CBC has been reported to reduce inflammation (in an animal model), CBG could potentially be used to treat bladder dysfunction, and CBN may be useful in the treatment of fibromyalgia.

In addition to the research being conducted on rare cannabinoids, novel cannabinoid analogues are also being developed. These are compounds that are active at cannabinoid receptors, but do not occur naturally. Usually, they are derivatives of natural compounds, and closely resemble them. These novel substances have the potential to exhibit interesting pharmacological profiles.

Exhibit 1: Potential therapeutic uses of cannabinoids.



Source: Minor Cannabinoids: Biosynthesis, Molecular Pharmacology and Potential Therapeutic Uses, Kenneth B. Walsh, Amanda E. McKinney and Andrea E. Holmes, Frontiers in Pharmacology, November 2021. https://www.frontiersin.org/articles/10.3389/fphar.2021.777804/full

Manufacturing approaches

Cultivation and extraction

The increase in demand for a variety of cannabinoid products has led to differentiation and innovation in manufacturing processes. The traditional method of producing cannabinoids, primarily THC and CBD, is to cultivate and process the cannabis plant. For some recreational users, this is the preferred approach. It is often considered the most 'natural' method and produces the dried cannabis flower, in a variety of strains, which can be smoked or vaped. However, this form of production can be unpredictable and labour intensive. Traditional farming has only a three-month growing season and is vulnerable to pests, disease and variations in weather. These factors affect the quality of the plant, the yield and the overall cost. While preferred by some, the flowers contain a mixture of cannabinoids, rather than a single active pharmaceutical ingredient (API).

Extraction of cannabinoids from the plant is the most common method of cannabinoid production for medical use. There are several methods to extract the cannabinoids from the plant; the most common method is extraction with organic solvents. The downside of this approach is that cannabinoids only account for approximately 5% of a cannabis plant's weight. This means that following extraction, 95% of a plant's mass becomes waste. Additionally, since rare cannabinoids, such as THCV, occur in very small amounts within a plant, the extraction of rare cannabinoids from plants is not commercially viable.

There is, however, innovation in cultivation. PharmaCann focuses on the cultivation of high-yield THC flowers for medical use. It has developed a greenhouse-based approach that reduces plant growth time to nine weeks and plants can be grown all year round. It recently raised US$40m in senior secured notes. BioHarvest Sciences (CNSX: BHSC, market cap US$160m) has a patented platform technology in which it isolates plant cells that produce desired products or metabolites,

such as cannabinoids. The cells are grown in a petri dish and once they reach a high enough mass, the cells are harvested to produce a powder containing the desired product. BioHarvest has shown the feasibility of its overall approach with its red grape cell product, VINIA. Its first cannabinoid product has been guided to be commercially available in 2022.

Chemical synthesis

Chemical synthesis is a viable manufacturing method for both common and rare cannabinoids. This is a lab-based process where a chemical entity is converted into another through a series of chemical reactions. This can be a preferred option to manufacture small quantities of a cannabinoid, as chemical synthesis can be conducted relatively efficiently on a small scale. Other processes may provide better cost efficiency for larger production volumes. Additionally, the viability of chemical synthesis depends on the cannabinoid. In some cases, both small- and large-scale synthesis will be well defined. In other cases, the synthetic route may be unknown and/or unviable.

Purisys is a leader in the manufacture of pharmaceutical-grade cannabinoids through chemical synthesis. It has a patented process for the synthesis of ultra-high purity CBD containing less than 0.001% THC. Ultra-high purity CBD comes with high costs of production; Purisys sells 100mg of CBD for US$400.

Recipharm, a pharmaceutical contract development and manufacturing organisation, has developed synthetic routes to manufacture rare cannabinoids including CBDA and cannabigerolic acid (CBGA). It claims to have the ability to rapidly produce small quantities of cannabinoids and that it can develop large-scale synthetic routes of an API at pharmaceutical-grade purity for clinical trials.

The synthetic forms of THC, dronabinol and nabilone, are both manufactured through chemical synthesis. They are both approved by the FDA for use by cancer patients to reduce chemotherapy induced nausea and vomiting.

Biosynthesis

Biosynthesis is a process that produces naturally occurring chemical compounds through successive enzyme catalysed reactions. Advances in bioengineering have led to methods to convert microorganisms into cost-effective and scalable 'microbial cell factories' that can produce molecules, such as cannabinoids. The bacteria *E. coli* and baker's yeast (*S. cerevisiae*) are often the microorganisms of choice to perform biosynthesis of useful, naturally occurring molecules. The genomes of these microorganisms are well understood, which allows bioengineering to convert these cells into molecule production factories. This is achieved through inserting specific enzymes into a microorganism and/or by modifying its genetics. This instructs the bioengineered microorganism to produce a specific molecule. As with plant cultivation and chemical synthesis, extraction and purification steps are required to collect the pure API.

Baker's yeast is generally regarded as safe for the production of biopharmaceuticals; in 1982, the FDA approved the use of bioengineered baker's yeast to produce therapeutic insulin. Throughout the biotech industry, both yeast and bacteria are broadly used for biosynthesis. However, some manufacturers state the use of bacteria instead of yeast can make the cannabinoid extraction process easier and more cost-effective on an industrial scale. Bacteria directly secrete the cannabinoid products into their surrounding medium, whereas yeasts must be separated from the cannabinoid molecules, following synthesis.

Overall, biosynthesis is seen by many as the most cost-effective and environmentally friendly method to manufacture industrial-scale cannabinoids although this remains an evolving value proposition. The microorganisms can convert sugar into cannabinoids and can be fermented in existing large-scale infrastructure such as bioreactors that are readily available.

Genomatica uses both bacteria and yeast to manufacture a variety of products including compostable packaging, cosmetics and cannabinoids. It focuses on renewable feedstock to grow its bioengineered microorganisms. Genomatica is partnered with Creo to produce CBG. In June 2021, Creo was issued a US patent for its proprietary method of manufacturing geranyl pyrophosphate, an essential molecule in the biosynthesis of many cannabinoids.

One of the older biosynthesis companies is Amyris (Nasdaq: AMRS; market cap US$1.4bn); it has been biosynthesising a range of products since 2003. It is positioning itself to become a market leader in large-scale, low-cost production of CBG. Amyris's Spain-based manufacturing partner is currently producing industrial-scale CBG using 225,000 litre fermenters.

In March 2021, Willow Biosciences (TSE: WLLW; market cap C$44m) completed its first commercial-scale fermentation of CBG. Willow has since increased production, currently fermenting CBG in 10,000 litre reactors. It has also reported that it has developed a process for biosynthesising the rare cannabinoid CBGA.

Founded in 2015, Demetrix has raised US$61m in funding to scale up its biosynthesis-based manufacture and isolation of cannabinoid products. In 2021, the company made its first CBG product available for sampling, and quickly moved to scale up production. Demetrix's R&D efforts are also focused on developing proprietary biosynthesis pathways for other rare cannabinoids.

Combined fermentation and chemical synthesis

As noted, there are a several companies that bioengineer and ferment bacteria or yeast to manufacture cannabinoids. BayMedica, a division of InMed Pharmaceuticals (Nasdaq: INM; market cap US$13.4m), also uses these means, along with chemical synthesis, to produce rare cannabinoids at food-grade GMP, primarily for the health and wellness industry. BayMedica's platform bioengineers baker's yeast to biosynthesise cannabinoids, which are isolated and purified. However, depending on the desired cannabinoid, purity, scale, chemical synthesis or a hybrid approach that may be the preferred route of manufacturing, BayMedica also modifies select cannabinoids to create novel chemical entities that are subtly different from naturally occurring cannabinoids but may have unique and pharmaceutically interesting properties.

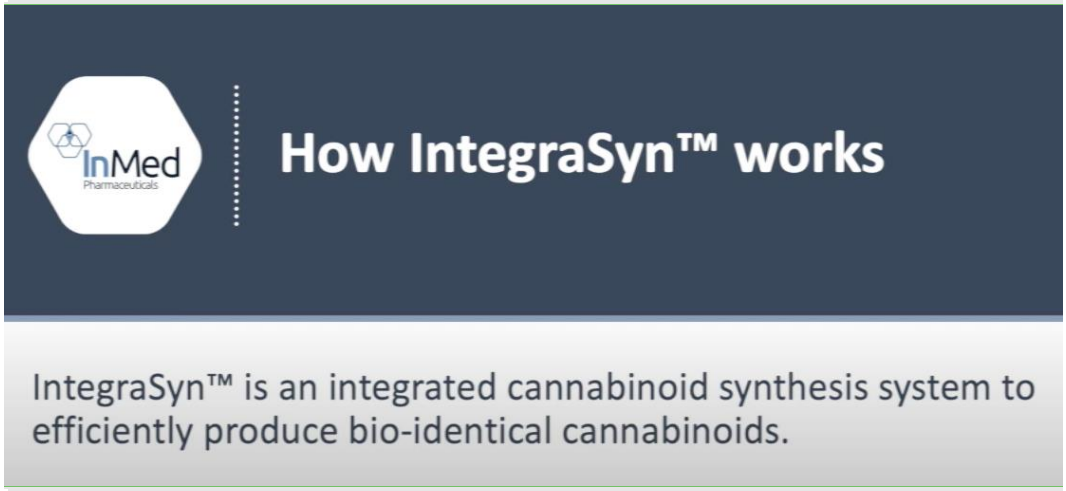
The additional advantage of its chemistry capability is that BayMedica can be agile in its approach to manufacturing. Depending on the cannabinoid and the scale at which it is produced, it can be more efficient and cost-effective to produce it by complete chemical synthesis, biosynthesis or a combination of the two. BayMedica's dual expertise allows it to select the best route for each product. BayMedica is currently a global leader in large batch production of CBC.

Enzymes for biotransformation

InMed Pharmaceuticals is focused on the production of rare cannabinoids for pharmaceutical use. It has developed a proprietary manufacturing process, IntegraSyn, that utilises biotransformation, the modification of a chemical compound by an enzyme. The company's IntegraSyn modular process begins with the fermentation of bioengineered *E.coli* to biosynthesize specific proprietary enzymes, rather than a cannabinoid. These enzymes are subsequently used to perform biotransformations on chemical substrates to produce rare cannabinoids, which can be separated and purified.

Unlike typical systems, the initial fermentation step does not produce a cannabinoid. Additionally, the fermented enzyme can be used in the biotransformation of multiple cannabinoid products. This makes the whole process more flexible, meaning that production can be shifted from one cannabinoid to another when there is need to. InMed also reports that the IntegraSyn process is up to 50% faster than yeast-based biosynthesis, which typically takes 5–10 days for cannabinoid synthesis. It also states that the process provides higher yields than traditional biosynthesis, or the chemical synthesis, of several cannabinoids.

Exhibit 2: Video of how IntegraSyn works



Source: InMed Pharmaceuticals.

Industry development and investment

Quality at a competitive price

We have noted that several companies, including Demetrix, Creo and Willow Biosciences, are aiming develop CBG products at industrial scale. As the market grows and eventually approaches saturation, competitive pricing and consistent purity will become increasingly essential for the success of cannabinoid manufacturers. This can be challenging for those manufacturers that are limited to smaller-scale production or whose processes do not benefit from larger scale efficiencies. Additionally, as the production of cannabinoids has multiple stages including synthesis, extraction and purification, high levels of quality control and specialist infrastructure are required. Therefore, many companies are turning to commercial manufacturing organisations (CMOs) to scale up production. An example of this is Willow Biosciences' partnership with CMO Curia. This approach reduces costs by making use of existing fermentation infrastructure and takes advantage of expertise in large-scale fermentation.

Manufacture of rare cannabinoids

With a growing demand for cannabinoids, the ability to produce a greater number of rare cannabinoids will become increasingly important across the industry. Of the rare cannabinoids, we have noted several companies focusing on the production of CBG. However, few have developed manufacturing processes for the other rare cannabinoids. BayMedica currently produces CBT, CBC and CBDV at large scale. The commercial-scale production of another rare cannabinoid, THCV, is underway. The company currently employs a chemical synthesis process on a scale in the hundreds of kilogrammes and claims to be able to ramp up production to metric tonnes, utilising the same process.

Investment from the pharmaceutical industry

There is significant investment in the pharmaceutical segment of the market. In 2021, Jazz Pharmaceuticals (Nasdaq: JAZZ; market cap US$9.7bn) acquired GW Pharmaceutical, a therapeutic cannabinoid company, for US$7.2bn. In March 2022, Pfizer (NYSE: PFE; market cap US$281bn) acquired Arena Pharmaceuticals for approximately US$6.7bn. The primary asset that Pfizer gained in this acquisition is Arena's drug candidate etrasimod, currently in Phase III trials for ulcerative colitis and in a Phase IIb/III programme for Crohn's disease. Pfizer also gained Arena's

cannabinoid drug candidate olorinab, which was previously evaluated for pain conditions associated with gastrointestinal diseases but did not meet the primary endpoint in a previous Phase II trial for irritable bowel syndrome. In September 2021, InMed commenced a Phase II clinical trial of INM-755 (cannabinol) to treat epidermolysis bullosa, a rare genetic disorder that causes skin to become very fragile. Additionally, InMed's formulation INM-088 (cannabinol) is in preclinical trials for potential use for glaucoma.

Partnerships and acquisitions

There have been several partnerships and acquisitions across the market that have enabled companies to gain scale-up or alternative manufacturing capabilities. Cronos Group and Ginkgo Bioworks entered a partnership to produce cultured cannabinoids. As part of this partnership, Cronos has acquired an 84,000 square foot fermentation and manufacturing facility. This is to enable the industrial-scale production of cannabinoids. In September 2021, InMed announced the acquisition of BayMedica for approximately US$4m. The combined company has multiple manufacturing capabilities to produce rare cannabinoids at both food and pharmaceutical grade. BayMedica provides expertise in yeast biosynthesis and chemical synthesis, while InMed provides its proprietary IntegraSyn platform and expertise in bacteria-based biosynthesis. This consolidation of manufacturing methods allows for an agile and adaptive approach to the production of rare cannabinoids.

Exhibit 3: Companies that manufacture cannabinoids

Company	Partner	Manufacturing method	Cannabinoid
InMed		Biosynthesis, biotransformation	Various
BayMedica		Biosynthesis, chemical synthesis	CBC, CBT, THCV, CBDV
Cronos group	Ginkgo Bioworks	Biosynthesis	CBG
Creo	Genomatica	Biosynthesis	CBG
Demetrix		Biosynthesis	CBG
Willow Biosciences	Purisys	Biosynthesis, chemical synthesis	CBG
LAVVAN		Biosynthesis	CBD, CBG
Amyris		Biosynthesis	CBG
Logos		Biosynthesis	CBG, CBC, CBD, CBDA, CBDV
CB Therapeutics		Biosynthesis	Various

Source: Edison Investment Research

General disclaimer and copyright

This report has been commissioned by InMed Pharmaceuticals and prepared and issued by Edison, in consideration of a fee payable by InMed Pharmaceuticals. Edison Investment Research standard fees are £60,000 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the research department of Edison at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Crown Wealth Group Pty Ltd who holds an Australian Financial Services Licence (Number: 494274). This research is issued in Australia by Edison AU and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

This document is prepared and provided by Edison for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document.

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

Edison relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia