MEDRx Co. Ltd

（4586 Mothers） Issued: March 23, 2022

Quietly Developing Blockbusters

Has proprietary know-how in a niche sector

MEDRx's business model involves the development of transdermal formulations of the active ingredients of existing oral and injection drugs, which development it then licenses out to pharmaceutical companies, from whom it collects milestone income and, after launch, royalties on sales. Compared to other drug discovery businesses MEDRx's activities have a greater probability of success because of its emphasis on existing active pharmaceutical ingredients, and, because of the niche nature of its activities there are limited competitors, from whom it is in any case distinguished by two proprietary technologies, ILTS® and NCTS®. It has also developed a microneedle technology on which feasibility studies are now being performed to provide 'vaccine patches'.

Significant decline in development in 2021

2021 was a slow year for MEDRx. The slowdown was particularly noticeable in the following three areas, in addition to which the expected milestone income did not materialise.

① It was expected that Lydolyte lidocaine tape would be the company's first product to market. However, in the event, it was unable to get the necessary approval and has to conduct further tests and re-apply.

② The process of selecting a sub-licensee for tizanidine tape (CPN-101; MRX-4TZT), which has been out-licensed to Cipla, is ongoing. This has delayed the start of Phase-2, which has been carried over to 2022.

③ Phase-1 clinical tests for memantine patches were scheduled for 2021. However, the difficulties presented by the Covid-19 environment, particularly the selection of a test drug manufacturer and the transfer of technology, has meant that tests have been delayed until 2022 (an application was submitted in 2021).

Despite the above. 2021 was a year in which steady progress was seen in the development of major product candidates.

Company quietly developing major product candidates

In August 2021, MEDRx announced it was going to start developing diclofenac-lidocaine tape (MRX-6LDT), which is expected to achieve blockbuster sales. Since in 2022 development funds were to be diverted to supplementary tests for Lydolyte, the development of MRX-6LDT only proceeded to the pre-clinical testing stage, with Phase-1 being held over until 2023 or beyond. However, with predecessor products paving the way the plan was for Phase-2 to be completed in around 2026 prior to a licensing-out. The expectation was that the licensing-out would occur against a backdrop of favourable market conditions. Further, in the high potential area of microneedles (vaccine patches) an upgrade to the test facility was completed in January 2021, focusing on bio-safety measures for the prevention of proliferation and thereby allowing the handling of pathogenic bacteria and viruses and genetically modified organisms. At present, feasibility studies are being undertaken by pharmaceutical companies and vaccine ventures at home and abroad. MEDRx hopes to confirm effectiveness on human subjects in 2023 and thereby significantly raise the interest of the big pharmaceutical companies. Looking ahead, if development proceeds smoothly, it is possible that a series of products will be ready for the market from 2024 onwards. The value of the company will be additionally enhanced by progress in the development of diclofenac-lidocaine tape (MRX-6LDT) and microneedles (vaccine patches). It is thought that the company's current market value only discounts the value of the Lydolyte lidocaine tape, which will probably be the first to the market.

Revised Basic Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Kagawa Pref.
President	Yonehiro Matsumura
Established	January 2002
Capital	JPY7,803 mil
Listed	Feb. 2013
URL	www.medrx.co.jp
Industry	Pharma
Employees	23 (consol.)
Key indicators (March 22 2022)	
Share Price	JPY115
52-week low	JPY94
52-week high	JPY327
Shares outstanding	24,595,100
Trading unit	100 shares
Market value	JPY2,828 mil
Dividend	0
Forecast EPS	-40.9 JPY
Forecast PER	na
Actual BPS	JPY77.09
Actual PBR	1.49X

On the basis of shares outstanding (excl treasury shares)

Results	Sales JPY-mil	YoY %	Op. Income JPYmil	YoY %	R.P. JPY mil	YoY %	Net Income JPY mil	YoY %	EPS JPY	Share Price (JPY) High	Share Price (JPY) Low	
17/12 Actual	198	787.2	-983	na	-988	na	-884	na	-103.2	1,345	453	
18/12 Actual	8	-95.8	-1,273	na	-1,285	na	-1,267	na	-126.7	2,060	425	
19/12 Actual	169	1922.9	-1,627	na	-1,633	na	-1,616	na	-134.3	698	301	
20/12 Actual	115	-32.2	-1,130	na	-1,152	na	-1,114	na	-68.6	426	160	
21/12 Actual	8	-92.7	-1,061	na	-1,074	na	-1,059	na	-49.6	327	126	
22/12 Forecast	289	3512.5	-1,002	na	-1,003	na	-1,006	na	-40.9			

Company Outline & Management Philosophy

A venture company engaged in developing transdermal absorption formulations

In broad terms, the company is engaged in developing transdermal absorption formulations using the active ingredients of existing oral and injectable drugs. It licenses out these formulations to pharmaceutical companies, collecting milestone payments and, after launching in the market, royalties on sales.

Transdermal absorption formulations make up a growing medium to long-term segment of the pharmaceutical market. Among their attributes are maximisation of pharmaceutical effect, reduced side-effects and better quality of life for the patient. These attributes are achieved by the following:

① Providing a consistent and sustained release of active ingredients: enabling the maintenance of a constant volume of the drug in the bloodstream.

② Little or no first-pass effect: while the efficacy of orally administered drugs can be reduced to 10-20% on passage through the liver, this is not an issue in the case of transdermal absorption formulations.

③ Better medication compliance: suitable for patients who find it difficult to take drugs orally due to problems swallowing, and also reduces the problem of forgetting to medicate.

④ Unlike drug delivery by injection, transdermal delivery is painless.

⑤ Transdermal delivery lends itself to a wide range of conditions.

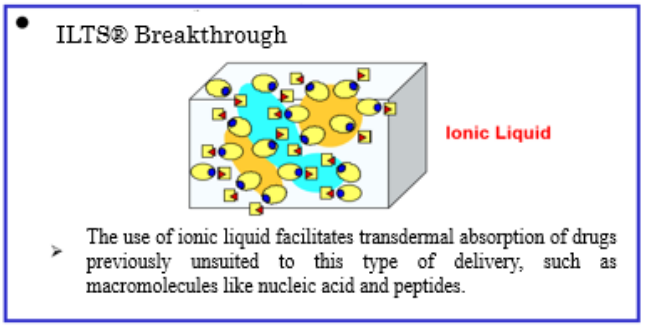
The company has proprietary technologies, giving its products a higher probability of success than is possible for other new drug discovery businesses

The MEDRx business model is distinctive in two ways:

(a) It is low risk (i.e. high probability of success) because it does not involve the discovery or development of new active ingredients.

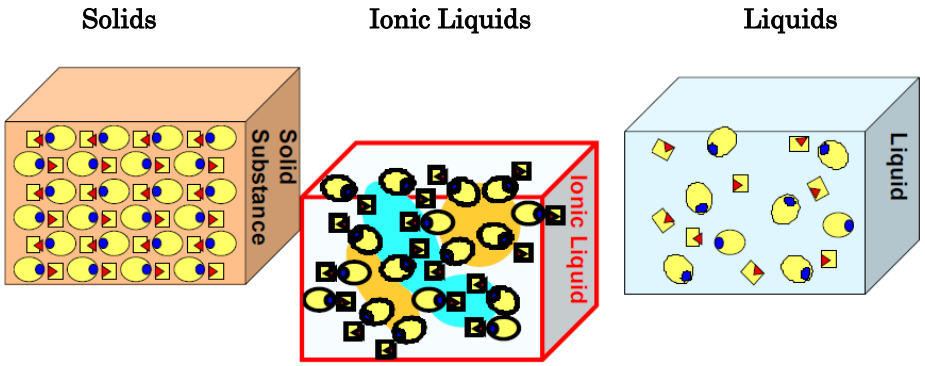
(b) The company has its own transdermal absorption technology using ionic liquids (ILTS®: Ionic Liquid Transdermal System), which distinguishes it from other companies.

Note: Ionic liquids are salts in liquid form at room temperature composed of ions which are resistant to crystalization. They are non-volatile, non-flammable and electricity conductive. In recent years these properties have led to applications in lithium battery electrolysis and elsewhere. With ILTS®, MEDRx was the first to develop the technology for the transdermal absorption of ionic liquids, thus facilitating the administration of drugs which are normally difficult to administer transdermally. With existing technology, transdermal absorption was difficult in the case of nucleic acid or macromolecular formulations, but ILTS® has made it much easier.



Source: MEDRx company briefing

The human skin is composed of the highly hydrophobic stratum corneum and the highly hydrophilic epidermal/ dermal layer. Highly hydrophilic active ingredients of drugs cannot permeate and diffuse in the stratum corneum. In ionic liquids, the anion or negative part (blue circle in the figure) is bonded to the hydrophilic group, and the cation or positive part (red △ in the figure) is bonded to the hydrophobic group. Such liquids thus have amphipathic properties (both hydrophilic and hydrophobic). Further, molecules do not move randomly as in ordinary liquids, but the structure is formed at the nano level when viewed from moment to moment. That is to say, the molecules that are ionic liquefied congregate (light blue elliptical and orange elliptical parts in the figure: alkyl congregation and clone congregation). According to the nanostructured fluid hypothesis, the active ingredients of a drug dissolve in an ionic liquid to a state analogous to enclosure in nanoparticles. The technique involved means that transdermal absorption of nucleic acids and high molecular weight drugs, which was difficult to achieve in the past, is now much easier.



Source: MEDRx company briefing

The company has a well-endowed library of ionic liquids and this know-how presents a formidable barrier to entry

A notable feature of MEDRx's ILTS® is that it has built high barriers to entry. The company has a library of several hundred ionic liquids formed from combinations of compounds with a track record of use on human subjects as pharmaceuticals and additives. The company also has extensive know-how on selecting ionic liquids for particular drug properties, and formulation expertise on maintaining and improving the transdermal properties of ionic liquids.

Mainly targeting the US market

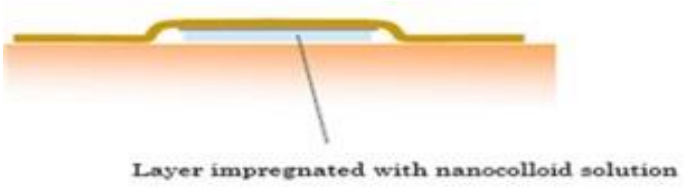
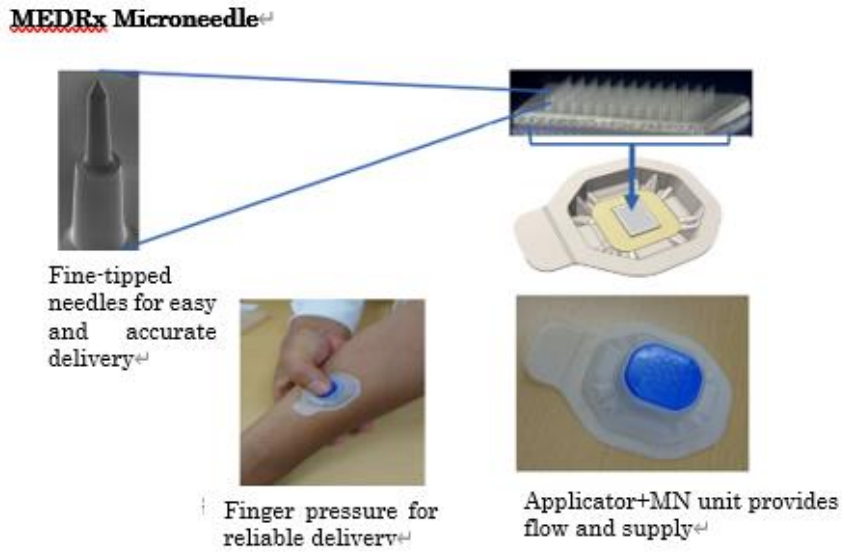
The company's primary target is the US market for transdermal absorption formulations, mainly because of the size of the potential market.

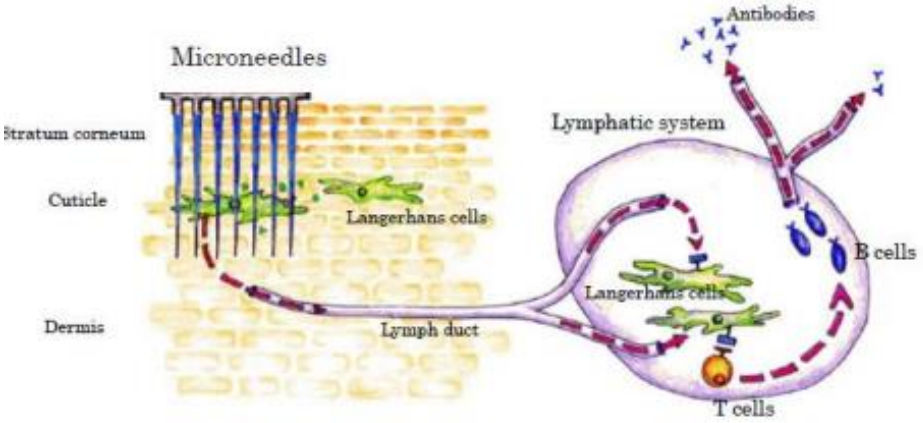
In addition, winning approval in the US for formulations using existing drugs does not require the pre-clinical testing necessary to submit an application for a new drug (while not true in all cases, after Phase-1 clinical trials, Phase-2 can be omitted and the process moves directly to Phase-3). Also worth bearing in mind is that patch and tape-type drugs tend to command higher prices in the US than in Japan.

There are five product pipelines to which MEDRx has applied its proprietary ILTS® technology

The main products to which the ILTS® technology is applied are tizanidine tape (CPN-101, MRX-4TZT), which has been successfully licensed out to Cipla Corp., lidocaine tape (MRX-5LBT), fentanyl tape (MRX-9FLT), oxycodone tape (MRX-1OXT) and diclofenac-lidocaine tape (MRX-6LDT).

The company also has a transdermal absorption technology using nanocolloids (NCTS®: Nano-Sized Colloid Transdermal System). As mentioned earlier, the ILTS® technology is used in the transdermal absorption of macromolecular agents such as peptides and nucleic acids. The NCTS® technology, however, enhances transdermal absorption of relatively low molecular-mass agents by reducing pharmacologically active components to nano-sized colloids. Among products now at the development

A memantine patch using NCTS® technology has been developed	stage for which information has already been disclosed is MRX-7MLL, a transdermal absorption formulation using memantine (for the treatment of Alzheimer's), which can suppress the skin irritation which memantine usually causes. **NCTS®: Nano-sized Colloid Transdermal System (image)**  Source: Fair Research Inc, using company briefing materials
The company has developed microneedle technology to provide "vaccination patches"	The company has also developed a technology using microneedle arrays as a sort of "vaccination patch". The microneedle technique works by using super-fine needles to open apertures in the surface of the skin, thereby allowing access to the drug. The skin not only acts as a physical barrier to foreign substances but also acts immunologically to expel such substances. Langerhans cells in the epidermis below the stratum corneum and dermis dendritic cells in the dermis below, are antigen-presenting cells which play an important role in biological defense. A strong immune response can be elicited by efficiently transmitting the vaccine antigen to these antigen-presenting cells. However, the stratum corneum presents a barrier, so that vaccine applied to the skin does not penetrate. Microneedles transmit drugs into the skin by opening apertures in the epidermis with superfine needles. They are less than 1mm in length and do not reach the nerve, hence providing vaccination without pain. In other words, this method can be seen as a " vaccination patch".  Source: MEDRx company briefing, February 2021 This business has important social ramifications. Not only does the 'vaccination patch' using minimally invasive microneedles entail less pain than an injection, but it can be

Microneedle technology provides a viable method for controlling pandemics in developing countries	patient-administered without the presence of the medical worker who would normally be involved. Additionally, microneedles to which solid vaccine antigens have been applied are very suitable for storage at room temperature, and are easy to transport. This makes the technology a promising means of dealing with pandemics in developing countries that may have only a rudimentary medical environment. **Microneedle technology (image)**  Source: Fair Research Inc. using various materials

Main product pipelines

The company has seven product pipelines, including five tape formulations, together with memantine patches and microneedles

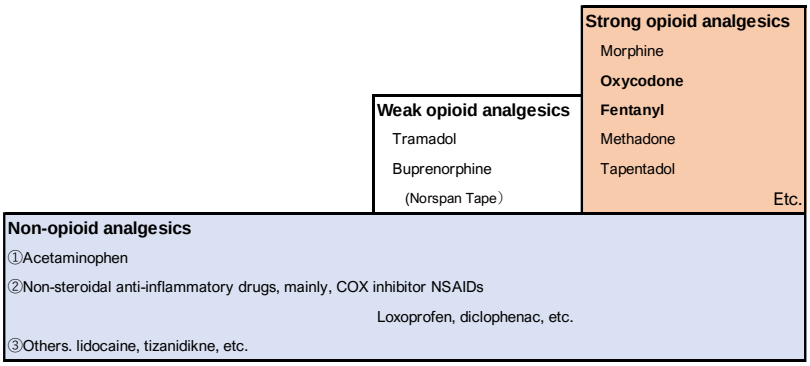
Currently, MEDRX's pipeline products consist of tizanidine tape (MRX-4TZT), lidocaine tape (MRX-5LBT), fentanyl tape (MRX-9FLT), oxycodone tape (MRX-1OXT), memantine patches (MRX-7MLL), diclofenac-lidocaine tape (MRX-6LDT) and microneedles. Five of these, excluding memantine tape, are for pain relief, and the development of oxycodone tape (MRX-1OXT) has been discontinued.

Main development pipelines

Product name Development Code	Drug Formulation Development	Pre Clinical	Ph-I	Ph-II	Ph-III	NDA	Launch
CPN-101(MRX-4TZT) Spasticity (Tizanidine, transdermal, ILTS®)				Worldwide licensing agreement (except for East Asia) with Cipla USA Inc. Phase 1b has got successful result. Phase 2 to be prepared			
MRX-5LBT "Lydolyte" Neuropathic Pain (Lidocaine, topical, ILTS®)				Receipt of Complete Response Letter Expected to get approval in 2023 after additional study			
MRX-9FLT Moderate-Severe Pain (Fentanyl, transdermal, ILTS®)				Fast Track designation Clinical Study on-going			
MRX-1OXT Moderate-Severe Pain (Oxycodone, transdermal, ILTS®)				Phase 1a has got result			
MRX-7MLL Alzheimer's Disease (Memantine, transdermal, NCTS®)			IND filing				
MRX-6LDT Chronic Pain (Diclofenac-lidocaine, ILTS®)							
Microneedles (MN)	Animal trials to study the feasibility of MN vaccine formulations for infectious diseases etc.						

Source: Company briefing, February 2022

Reference: Types of analgesic



Note:

Acetaminophen act on the central nervous system

NSAIDs mainly act on the peripheral nerves

Lidocaine is a local anesthesia that blocks sodium channels in the nerve membrane, reversibly suppresses the conduction of action potentials in nerves, and blocks sensory and motor nerves.

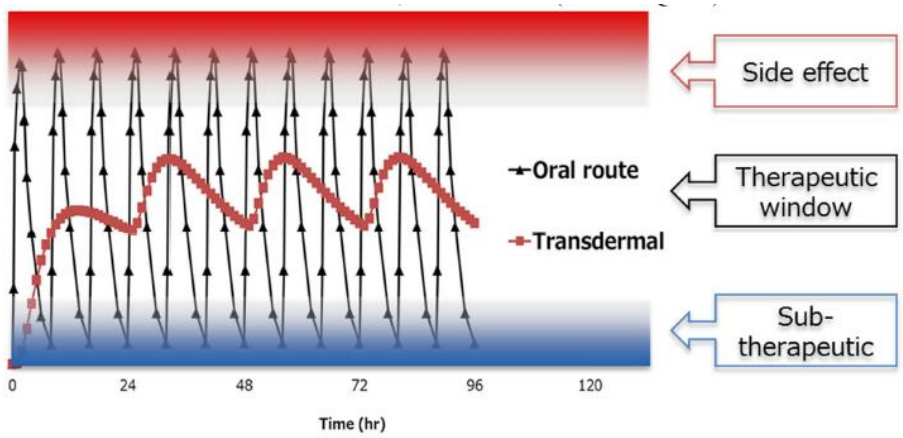
Tizanidine suppresses the release of excitatory transmitters, dilates peripheral blood vessels, and relieves muscle tension and pain by stimulating α2 receptors in the vasomotor center of the medulla oblongata.

Source: Fair Research Inc. using various sources

1. Tizanidine Tape: MRX-4TZT (CPN-101)

Tizanidine is a central muscle relaxant sometimes used to relieve stiff shoulders. There is no competing patch product

Tizanidine tape, CPN-101 (MRX-4TZT) employs tizanidine (sold as Zanaflex), a central muscle relaxant used also for relieving shoulder stiffness, rendered transdermal by ILTS®. It works on the brain/central nervous system, unlike lidocaine or ETOREAT® which work at the local level (peripheral nerves and muscle), where blood concentration produces medicinal effects. Judging from the results of Phase-1a tests (Phase-1 clinical trials exploration phase) conducted in the US in February 2017, tizanidine tape provides the same level of sustained tizanidine in the bloodstream as the oral preparation with less drowsiness or other side-effects.



Note1: Since the concentration in the blood of the oral preparation shows a spike-type dynamic that rises and falls rapidly after administration, it can rise excessively to a level where side effects occur.

Note 2: With transdermal preparations, the skin gradually absorbs the drug (sustained release), so the blood concentration in the therapeutic window can be maintained and the risk of side effects can be reduced.

Source: MEDRx company briefing

Phase-1a was completed in February 2017, and in April 2017 it was licensed out to Cipla

At the present time, tizanidine is only available in oral form – there are no competing patch or tape-type products. The US market for muscle relaxants in 2020 was valued at around JPY110 billion. After successful Phase-1a tests, in April 2017, the company concluded a development and sales licensing agreement with Cipla USA, the wholly owned subsidiary of the major Indian pharmaceuticals company, Cipla, covering the global market except for East Asia. (Subsequently, due to restructuring within the Cipla Group, the contractual partner changed to Cipla Technologies, LLC., hereafter referred to as Cipla.) Cipla made a lump-sum contract payment of JPY160 million in 2017 and appears to have agreed to milestone payments of up to USD30 million and, after launch, stepped royalties in proportion to sales. In January 2018, it was announced that supplementary Phase-1a' tests were in line with expectations. The plan was then to scale up the production of the test drug in 2018 and to conduct additional tests of repeat doses (Phase-1b pharmacokinetic tests and Phase-2 pharmacodynamic tests).

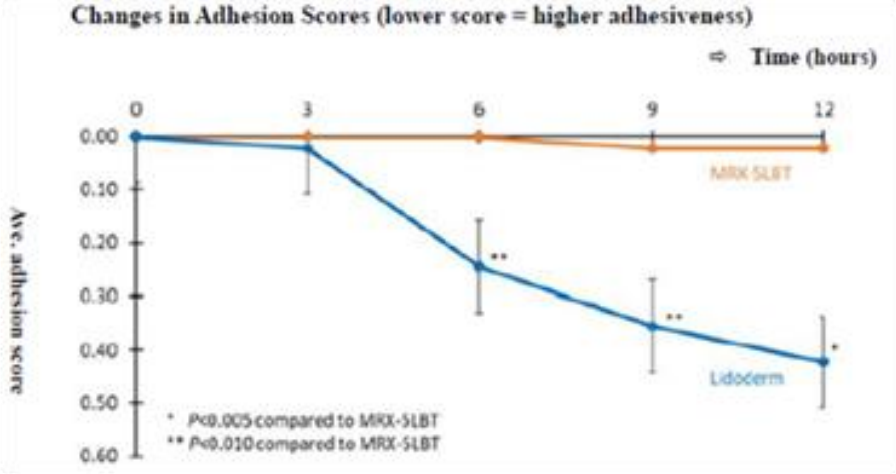
Repeat dose tests (Phase-1a') began in September 2017 and it was expected that the product would move on to the next testing stage in the second half of 2018. However, deveopment was interrupted by delays to the scaling up of production in the Autumn of 2018

However, the scaling-up of production took longer than expected and Phase-1b could not be undertaken until early 2019, with successful results in September. MEDRx originally anticipated a milestone payment of USD6 million with the success of this phase but, due to circumstances at both Cipla and MEDRx, the 2019 milestone was reduced to USD1 million.

This led to Cipla changing the milestone schedule

The plan was then for Cipla to lead Phase-2 trials for about 6 months from mid-2020 to

Phase-2 has been delayed by the effects of the COVID-19 pandemic, but it appears discussions are now ongoing to conclude a sub-licensing arrangement in 2022	investigate the pharmacological effect and drowsiness or other side-effects of dose increases on a small number of patients. However, due to the effects of the Covid-19 pandemic the transfer of technology to produce the test drug was delayed, and additionally Cipla changed its CNS development strategy during 2020 to put more stress on sub-licensing, away from in-house development. As a result of deliberations between the two parties, MEDRx was to handle preparations for Phase-2 while the selection of the sub licensee and various discussions have been ongoing. It appears that discussions are now continuing with a view to a sub-licensing agreement in 2022. It is surmised that the USD5 million milestone yet to be paid will be staggered: USD2 million in 2022, and USD3 million in 2023.
Lidocaine tape, for the relief of post-herpetic neuralgia (nerve pain following shingles), looks like becoming MEDRx's first product on the US market	**2. Lidocaine tape (product name: Lydolyte)** Lidocaine tape is one type of local anesthetic developed to treat post-herpetic neuralgia. A new drug application for lidocaine tape has already been accepted by the FDA and it is now being examined. It seems likely that it will be the first MEDRx product to make it to the US market. Shingles is a painful disease that develops when the varicella-zoster virus latent in the dorsal root ganglion is reactivated. For most patients treatment of the accompanying pain is available. Normally, the virus is blocked by immune cells and is dormant, but it reactivates when the immune system is weakened due to aging or chronic diseases. It used to be that the main treatment was nerve-blocking drug therapy, but in March 1999 Lidoderm®, a transdermally absorbent pad preparation was authorised in the US and subsequently experienced strong growth as the treatment of choice. The FDA authorisation at first applied only to nerve pain following shingles, but it has since been widely used off-label to treat neuropathic pain. Lidoderm® once enjoyed revenues of USD1.2 billion on sales of over 140 million pads. In 2014 Lidoderm went off-patent and competition increased from generics and from the appearance of numerous low-concentration OTC versions, such that in 2020 the US market for lidocaine pads was around JPY27 billion, 70% of which was accounted for by Lidoderm generics (in volume terms the proportion was 90%).
Lydolyte has three features which distinguish it from Lidoderm and generics	MEDRx is targeting this market by developing a product with the following three competitive advantages: ① Lydolyte is in tape form and therefore easier to use than pads ② Lydolyte uses less lidocaine (30% of that used in conventional products) for the same efficacy ③ Little skin irritation and superior adhesion, which is maintained while engaged in activity (does not detach due to perspiration) Tests in 2019 showed that adhesiveness was superior to that of Lidoderm®, and in the same year it was demonstrated that there was less skin irritation.

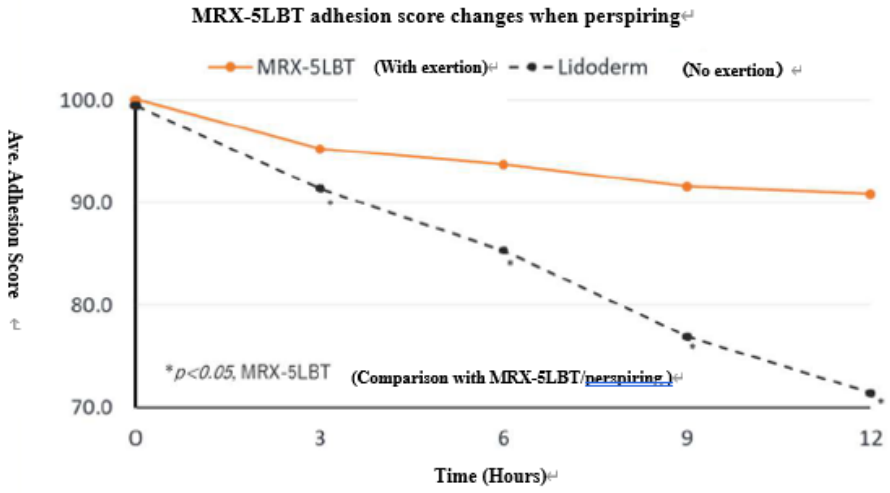


Source: Company briefing

Further, in January 2021, in tests on the effect of vigorous exercise (adhesiveness evaluation) it was shown that sufficient adhesion was maintained even when perspiring.

A new drug application made in August 2020 was not approved

The need for additional tests has emerged and a re-submission of the application is planned for the second half of 2022, or the first half of 2023 at the latest



Source: Company briefing

No. 2 in the tape formulation market – forerunners expanding

MEDRx completed all the tests required for an application in February 2020, and in August made its submission which was formally accepted by the FDA in October. However, on July 5 2021 MEDRx was in receipt of a Complete Response Letter (a notification that the examination was completed) from the FDA. Authorisation was not granted at this point and MEDRx initially surmised that further tests were not required and that, if appropriate responses were made to a number of queries posed by the FDA, authorization would come within 2021. In subsequent discussions with the FDA, however, it became clear that a number of additional tests to obtain approval were required. At present the company is going over details on these additional tests with the FDA with a view to conducting them in the second half of 2022 prior to re-submitting an application in the second half, or the first half of 2023 at the latest. It expects approval to be granted in 2023 and market launch to occur in 2024.

Reference: In July 2021 the FDA issued a new "Draft guidance for transdermal adhesion systems." It describes the level of adhesiveness required and makes a number of points related to the tests, such as adhesive properties when exercising, sweating, or taking a shower, and resistance to peeling off when rubbed against clothes or bedding.

Lidocaine tape already exists in the US. In October 2018, the US company Scilex Pharmaceuticals Inc., a subsidiary of Sorrento Therapeutics Inc., launched ZTlido®, a lidocaine tape with superior features to Lidoderm®. ZTlido® has sales in excess of 6 million tapes a year and is aiming for 10 million tapes to give it a 10% market share. It is thought that Lydolyte (MRX-5LBT) could achieve sales of JPY2-3 billion 2-3 years after launch. MEDRx is now seeking out a number of sales partners.

ZTlido® sales trend

(million USD)

2018	2019				2020				2021			
4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q
2.6	2.9	4.7	3.8	9.7	5.2	5.8	7.8	7.5	7.0	7.8	7.5	6.2
				Year				Year				Year
				21.0				26.3				28.5

Source: Fair Research Inc. using Sorrento securities filings

On April 16 2020 MEDRx concluded a joint research and development agreement with D. Western Therapeutics (DWTI). Under this agreement MEDRx will receive a total of JPY200 million from DWTI as milestones according to progress in commercialization in the US. JPY100 million will be payable upon application for authorization in the second half, and the remainder upon the receipt of authorization. After market launch a share of the royalties income will be payable to DWTI .

3. **Fentanyl Tape（MRX-9FLT）**

Fentanyl patches are widely indicated for medium to severe cancer pain

Fentanyl is a form of opioid indicated, usually in patch form, for the alleviation of severe acute pain, chronic pain and cancer pain. Since it can be administered transdermally it is often used in patch form for medium-severe cancer pain for patients who are unable to swallow, and since it is less likely to cause drowsiness or constipation it is indicated for patients who have had an adverse reaction to other opioid analgesics. However, there are occasions when fentanyl is replaced with a different drug due to the limited number of receptors in the body.

The US market size stood at JPY21 billion in 2020

The US company Alza was the first to develop patch formulations. Due to the success of this development, Alza was absorbed by Janssen in 2001 through a USD10.5 billion share exchange with Janssen Pharma (J & J's pharmaceutical arm). Janssen's US sales of the Duragesic® fentanyl patch exceeded USD2.4 billion (JPY260 billion) just before it went off-patent in 2004. The price per patch has since come down to below USD10, and the US market size in 2020 stood at around JPY21 billion (mostly generics). As described later in the section on oxycodone tape, in the US since 2017 the opioid crisis has led to increasing regulation, and the market for fentanyl patches is also contracting. However, cancer pain will not disappear, meaning that the market for what is an essential drug will maintain a certain size.

The FDA sees the prevention of misuse by infants and children as an important and valuable goal

However, with conventional fentanyl patches there are a number of fatal accidents annually caused by infants and children mistakenly chewing on or attaching used and discarded patches. The authorities are very concerned about this. The new fentanyl tape being developed by MEDRx uses a technique to prevent accidents. In an exchange in May 2019 the FDA clearly stated that this was an important and worthwhile goal in fentanyl tape development. In November 2019 MEDRx announced that fentanyl tape (MRX-9FLT) was the company's new product pipeline.

The background to fentanyl tape development

- Fentanyl is an opioid classified as a medical narcotic, and is used mainly in patch form to treat severe acute pain, chronic pain and cancer pain
- With existing products there have been reports of infants and children dying after chewing or and attaching used and discarded patches

- MRX-9FLT is a new tape which uses the company's proprietary know-how to control and prevent accidental use
  - At an interview meeting in May 2019 the regulatory authority, the FDA, noted that preventing accidents to children from the misuse of fentanyl was an important and worthwhile goal
- In 2018 the US market for fentanyl patches was valued at around JPY34 billion
  - Company thinks the added value of its accident prevention technique should help it to seize and expand its share

Source: MEDRx: "Supplementary explanation of capital raising", Nov.15, 2019

PK tests started in 2020

In March 2020 the company filed an application to conduct clinical trials and began those trials in July, with the first results becoming available in September. These included pilot pharmacokinetic (PK) tests to provide preliminary confirmation of blood concentration and dynamics. It was ascertained that the patch provided the same blood concentration as the reference drug, Duragesic®, and preliminary confirmation was made of the product's usefulness in deterring and preventing misuse and abuse.

Accorded fast track status in July 2021 now undergoing Pivotal bio-equivalence tests

After consulting with the FDA the company plans to conduct a series of safety tests and accidental misuse prevention tests, ready to submit an NDA in 2024

As noted earlier, the prevention of accidental misuse of fentanyl patches is of considerable importance and the FDA gave MEDRx's product fast-track status in July 2021. During 2022, after completing Pivotal BE tests to show biological equivalence with the reference product, Duragesic®, and after receiving FDA guidance on test design, the company will move on to skin safety tests and tests of the product's ability to prevent accidental misuse. It should than be able to submit an NDA at an early date in 2024. It is thought it will be possible to license out after the accidental misuse test design has been decided.

4. Oxycodone tape

Until three years ago oxycodone tape was expected to become MEDRx's biggest product

Until three years ago oxycodone tape was expected to become MEDRx's biggest product The company had rendered oxycodone, which has the highest share of the analgesic market in the US, transdermal with the use of ILTS® technology, and had further applied its AMARTS® methodology for preventing abuse and misuse, to create oxycodone tape (MRX-1OXT).

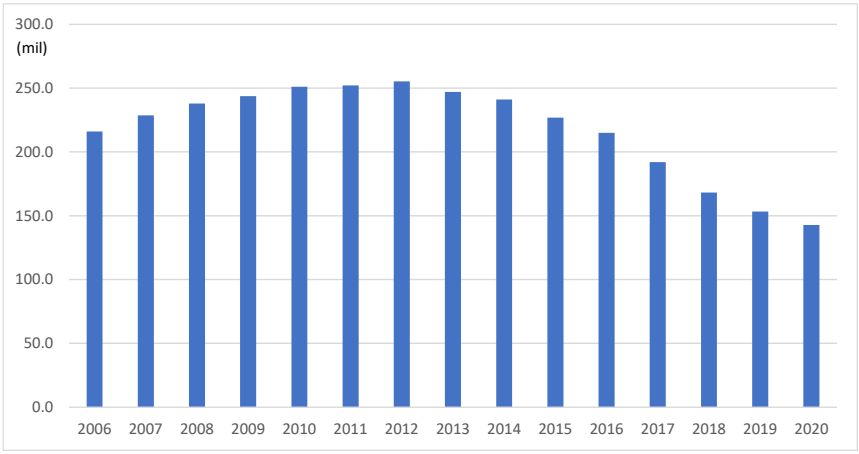
In the United States some 18 million patients have to take opioid prescriptions for protracted periods for pain management, so we believe it is unlikely that the need for opioid formulations will disappear. However, the authorities have focused on the development of pharmaceutical formulations which include methodologies to prevent abuse and misuse. In February 2018, the company completed Phase-1 of clinical testing in the US and announced that it seemed likely blood stream concentration was sufficient for pain management. It further disclosed it was working on improving absorbability, creating a smaller patch that was still able to provide an effective volume in the blood stream, and improving adhesiveness. We believe the company will start dose escalation trials (supplementary Phase-1 trials) in the second half of 2019 for possible completion around the end of 2019.

Note: Opioid is the general term for opium-like substances (not opium) with narcotic properties such as morphine, and is widely used for treatment of moderate to severe pain, as well as anaesthesia and cough suppression.

However, the abuse and misuse of opioid analgesic drugs has reached critical levels (the opioid crisis) and around the country a number of pharmaceutical companies have been taken to court. The authorities are also taking longer to investigate newly developed analgesics.

In the United States, the abuse and misuse of opioid annalgesics became a social problem. Because MEDRx's product uses proprietary technology to prevent abuse and misuse it was thought to be in a good competitive position. However, the volume of legal actions against opioid makers have made it difficult for MEDRx to find a licensee

Opioid analgesic prescriptions written in the US



Source: Fair Research Inc. using the CDC's U.S. Opioid Dispensing Rate Map

It was decided that, in the abence of regulatory approval a licensee could not be found, and therefor further development was halted

Eventually, in September 2019, Purdue Pharma, the manufacturer and distributor of an extended-release form of oral oxycodone known as OxyContin®, was forced into bankruptcy by the financial burden of awards made against it in a series of lawsuits. And by 2020, the market environment had changed to such an extent that opioid-type prescriptions written were 44% down on a YoY basis than at the peak in 2012.

The situation for new opioid-type drugs has thus became less and less clear, while the risk arose of being unable to find a licensee in the absence of FDA authorisation. With Oxycodone tape (MRX-1OXT) it seemed likely that there would be a focus on side-effects not only in Phase-2 but also in more extensive Phase-3 tests. For MEDRx, the financial burden of going it alone looked formidable. For that reason, the company suspended further development. The need for a major product to take its place thereby surfaced and fentanyl tape (MRX-9FLT) presented itself.

5.Memantine patches (MRX-7MLL)

Using an Alzheimer's drug in patch form is very significant

MRX-7MLL is the Alzheimer's drug memantine which MEDRx has rendered into patch form using NCTS®. Patches offer a number of advantages: drug administration is visible and is required once every three days or seven days, compared to the once-daily frequency of the oral preparation. Due to the introduction of generics the US market for oral Memantine has shrunk from around JPY75 billion to around 12 billion, but MEDRx believes the functionality of the patch formulation is such that it has no competition from generics and can command a comparatively high price.

The donepezil (Aricept) patch has already received regulatory

The company had been developing a patch (MRX-5DML) utilising NCTS® technology and combining donepezil (brand name: Aricept) and memantine. In the US, however, the sales volume of the two-drug combination was disappointing, while prescriptions for single-agent oral memantine and oral donepezil were strong. For this reason, the

approval	company switched to the development of patches using the memantine monotherapy MRX-7MLL and the donepezil monotherapy. A number of companies (Corium, Nitto Denko, Hisamitsu Pharmaceutical) have moved ahead in the development of donepezil patches, and since NCTS® technology can be more effectively employed with memantine, that is the drug MEDRX is proceeding with. In July 2018 the company started non-clinical studies in Japan (on March 14, 2022 Corium announced that it had received FDA approval for its ADLARITY® donepezil patch).
MEDRx has chosen to develop memantine in patch form	
Non-clinical tests of the memantine patch have already been completed. Since Phases 2 and 3 are unnecessary the selection process of a company in the US to undertake commercial production was carried out, but there has been a slight delay concluding this due to the COVID-19 pandemic	In December 2018, the FDA said, in response to a pre-clinical guidance request, that the content of the current non-clinical trials would be sufficient to begin Phase 1, and further, that if bioequivalence with oral memantine could be demonstrated, Phase 2 and Phase 3 could be omitted. The company therefore believes that a relatively early NDA is possible. The company is currently preparing to submit a clinical trial application for MRX-7MLL, having completed non-clinical studies in 2019. Since Phase 2 and Phase 3 are unnecessary the company has been seeking to select a manufacturing subcontractor and transfer technology in anticipation of commercial production. However, delays were caused by restrictions on travel between the US and Japan in the context of the COVID-19 pandemic, and an IND was finally submitted only in November 2021. Pharmacokinetic studies (in two stages) will be carried out in 2022, followed by bioequivalence studies, skin safety and long-term stability tests in 2023, before the submission of an NDA scheduled for in or around 2024.
Clinical trials starting in 2022	

Reference

US Alzheimer's drug treatment market: around JPY52 billion

of which, oral memantine around JPY12 billion

Source：MEDRx company briefing Feb. 2022

Note: Donepezil and memantine are the most common Alzheimer's drugs, mostly generics

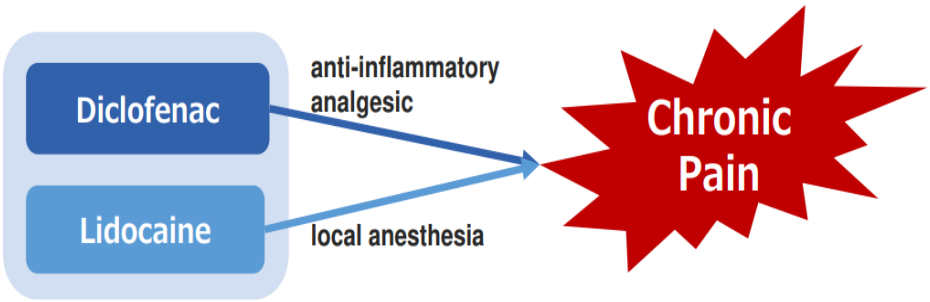
6.Diclofenac-lidocaine patches（MRX-6LDT）

On May 18 2021, MEDRx announced plans to develop a new pipeline, MRX-6LDT. This is a tape product using MEDRx's own transdermal drug technology, ILTS®. The tape allows simultaneous transdermal absorption of both the anti-inflammatory analgesic diclofenac, and the local anesthetic, lidocaine. At present there are no tapes or patches providing both diclofenac and lidocaine, and no-one else is developing one. At its briefing in August 2021 the company announced that pre-clinical studies were about to begin.

No other companies are developing patches using both diclofenac and lidocaine

MRX-6LDT characteristics

MRX-6LDT contains diclofenac and lidocaine, which work on pain in different ways, and the expectation is that they will have a supplementary or synergistic therapeutic effect (see illustration below).



Source: MEDRx: Financing - supplementary financing explanation, May 2021

Hisamitsu Pharmaceutical is developing in the United States (now Phase-3) a patch which provides a high level of diclofenac in the bloodstream to treat the pain of osteoarthritis of the knee

By using ILTS® technology, MRX-6LDT aims to achieve a level of diclofenac percutaneous penetration that is several times higher than that of conventional diclofenac patches widely used in Japan and other countries. Currently, Hisamitsu Pharmaceutical is developing a diclofenac patch (HP5000) for the pain caused by osteoarthritis of the knee (knee OA) in the US, where it is now at Phase-3 (NCT04683627). Hisamitsu has disclosed (November 2019) that in Phase-2 trials in which a high concentration was delivered to the affected part, results pointed to effectiveness and safety. Also, in March 2021, Hisamitsu's diclofenac patch (Dictor (R) tape for the alleviation of cancer pain) was authorised in Japan. The concentration of diclofenac in this tape is, at 75mg per tape, about 5 times that of commercially available diclofenac patches. While the volume of diclofenac in HP5000 has not been disclosed we assume it might be around the same level as Dictor ® tape. MEDRx is probably intending for MRX-6LDT to deliver a high volume of diclofenac to the affected part

MEDRx aims to deliver high levels of diclofenac and lidocaine to the affected body part

Meanwhile, regarding lidocaine, MEDRx appears to be considering a formulation that has a transdermal penetration rate that is several times higher than that of Lydolyte (lidocaine tape), for which the company is currently planning a re-application. Even at several times that of Lydolyte, it will still not reach the blood concentration at which side effects occur with injections, so it is expected that sufficient tolerability will be ensured.

Development schedule

Pre-clinical trials begin in 2022

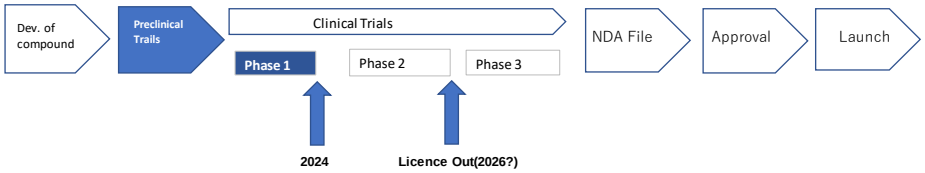
Phase-1: 2023～2024

Phase-2: 2025～2026 (expected)

Formulation development for MRX-6LDT has now been completed. At the company briefing held in August 2021, it was explained that the pre-clinicals were to start shortly and that Phase-1 would be carried out in 2022. However, authorisation of Lydolyte (lidocaine tape) required additional testing so the situation at present is that pre-clinicals are scheduled to start in 2022. Phase-1 trials are to begin 2023, testing safety, tolerability and confirming absorption of the drug in the body (blood concentration, etc.). The Phase-1 trials should last until 2024, following which, in order to confirm indications and responses, three or so clinical indications will be selected to ascertain responses by

administering the drug to several dozen cases per indication for 2-3 months (Phase-2). We assume the company is intending to license out after the effects have been evaluated (around 2026). Phase-3 trials of HP-5000 will be completed in December 2022, ready for the submission of an application in 2023. That being the case, in the period 2024-2026 sales of HP-5000 will pave the way in the Knee OA market and provide a tail wind for diclofenac patches at just the right time for the licensing-out of MRX-6LDT.

Hisamitsu Pharmaceutical's expanding diclofenac patch sales will pave the way for a licensing-out



Source: Fair Research Inc.

Targeted indications

Ultimately, the aim is to use it as an anti-inflammatory analgesic agent for a wide range of chronic pain, but the initial clinical indication to which it is likely to be targeted is knee osteoarthritis (Knee OA). The difficulty of developing analgesics was highlighted in the case of the Etoreat® tape, which failed because of reliance on how individuals feel as the endpoint for measuring drug effectiveness. Individuals feel pain differently and allowing for that can be the difference between success or failure in drug development. The level of pain from Knee OA is said to be easier in this respect. It seems very likely that development will start with this and, if successful, will expand to lower back pain, for which major demand is now served by Oxycodone, and other indications.

First indication expected to be knee osteoarthritis

Pain level felt used to measure effectiveness

The patient's pain level is ascertainable in the case of Knee OA

The last line of treatment for Knee OA is currently surgery for replacement with artificial joints (regenerative medicine with autologous cell culture is also available but is more expensive). Before reaching the surgery stage the main line of treatment is pain relief. In the last ten years opioids and non-steroidal anti-inflammatory drugs (NSAIDs) have played a major role and are used by most patients. Opioids, however, are addictive and can lead to abuse. Likewise, long term use of NSAIDs can give rise to side-effects related to the digestive system and cardiovascular system. There is thus a need for the development of drugs with a new action mechanism.

The final treatment for Knee OA is surgical replacement with an artificial joint, before which pain management is the main therapy

Pain suppression using opioids or non-steroidal anti-inflammatories can be problematic

At present, development of a number of new drugs is underway. The development of anti-NGF antibodies is attracting the most attention, but with a chequered history. Astra-Zeneca suspended the development of MEDI-578 at Phase-1 (in 2012), AbbVie terminated ABT-110 at Phase-1 (2013), J&J abandoned fulranumab at Phase-3 (2016), Astellas Pharma suspended ASP6294 at Phase-2 (2020), and Regeneron/Teva (Mitsubishi-Tanabe) proceeded as far as Pivotal trials but suspended fasinumab at administration trials (2020) and is now considering how to proceed. In addition, Pfizer-Lilly's very promising tanezumab received a negative rating from the FDA's Drug Safety and Risk Management Advisory Committee at Phase-3 in May 2021. (In the case of anti-NGF antibodies an increase in joint inflammation and bone infarction have been a not uncommon cause of suspension on safety grounds.)

At one point, the development of anti-NGF antibodies looked promising, but development was halted due to side effects.

In addition, studies have been done into a radical treatment by directly administering m-RNA of the cartilage-inducing transcription factor RUNX1 which induces the regeneration of knee cartilage into the knee joint. However, research is still in the early stages.

For the time being, opioids and non-steroidal anti-inflammatories will continue to be the main drugs used

Hence, the development of OA progression-inhibitors, which would reduce the need for analgesics, is still in the early stages. It seems therefore that opioids and NSAIDs will continue to play a central role in OA treatment for a while yet.

7. Microneedles

Since the 1990's advances in micro-fabrication technology have helped support research and development of microneedles

Although the microneedle concept has been around since the mid-1970's manufacturing technology and considerations of cost effectiveness have been sticking points. However, with advances in micro-fabrication technology since the1990's there has been a lot of progress in microneedle research and development.

There are four types of microneedle. One is the hollow microneedle. Like the standard injection needle, it has a hollow cavity into which the antigen solution is inserted prior to administration. Another involves the use of solid microneedles in an array to puncture the skin, following which the needles are removed and the vaccine antigen applied. Since both methods use a liquid containing the vaccine antigen, they require cold chain logistics in the same way as standard vaccines, and this has stymied widespread acceptance. A third method involves the use of a microneedle array, the surface of which has been coated with dried vaccine, to puncture the skin. Since the vaccine is not in solution but in a dried state it is highly stable. Microneedle arrays can be used for the administration of live vaccines. This is the methodology being pursued in Japan by MEDRx and Nipro Pharma and, overseas, by 3M. To improve safety (e.g. to reduce the danger of a broken needle remaining in the body) efforts are being made to make microneedles using biodegradable polymers. The products being made differ in terms of the shape of the needles, the density of the needles per unit of skin surface, and the coating solution. In the fourth type of microneedle, being developed by Fuji Film, the vaccine antigen is kneaded into the microneedle, the biopolymer needle point in the skin then decomposes and the antigen is released.

The key is easy and reliable drug administration

MEDRx has for the past 16 years been doing research on microneedles in an effort to find a simple and reliable way of administering drugs. This means the needle must reach the dermis vertically and painlessly, but the key is in the shape of the needle tip and the attachment device (the applicator). In the case of 3M and Nipro, the applicator is spring-loaded and pushed in, so more force is applied and the patient may feel pain, while the MEDRx device requires only hand strength. The shape of the MEDRx microneedles is patented, and the applicator's patent has been registered in Japan and China. MEDRx also aims to secure rights in the US, Europe, India and Brazil. In addition, MEDRx is also applying for a patent in the US, Japan and China covering the technology for securing the needles in the skin, which is needed to achieve easy and reliable drug administration.

Source: MEDRx company briefing, February 2022

Two US companies are leading the way in medical microneedles

Zosano submitted for approval a migraine product but this was not approved and supplementary tests are now being carried out

There is currently a lot of work going on worldwide to develop medical products using microneedles. This has recently been seen in the development of COVID-19 vaccines in response to the new corona virus pandemic. However, two US companies, Zosano and Radius, leading the say in medical applications, have been developing formulations for non-vaccine applications. In December 2019, Zosano submitted an unsuccessful NDA for a migraine treatment using microneedles. The company is now in discussions with the FDA on supplementary tests. In the case of Radius, their osteoporosis treatment was in Phase-3 but it appears to have abandoned development of a current generation microneedle after failing in December 2021 to demonstrate non-inferiority versus injectables. It seems that microneedles generate varying doses and stabilising the necessary amount is proving difficult.

Radius's osteoporosis product failed at Phase-3

In Japan in December 2021, the Hokkaido University Hospital used microneedles to vaccinate 39 subjects against Japanese encephalitis. It was reported that this method was 10 times more effective than the conventional subcutaneous injection method (Phase-1). It is thought the microneedles used were those that dissolve in the body, developed by Fuji Film.

In Japan, there have been doctor-initiated clinical trials in which Japanese encephalitis vaccine was administered to human subjects using microneedles

(Ref. 1) Zosano's Qtrypta™ (to treat migraine)

Applicator to facilitate entry of microneedle into the skin

(Ref. 2) Radius's ABALOPARATIDE-Patch (Failed at Phase-3)

Note: TYMLOS®: Microneedle and applicator to inject osteoporosis drug (coin indicates size)

MEDRx is also planning to target vaccinations

MEDRx envisions using microneedles mainly for the administration of vaccines. The vaccine business, however, depends on large volumes and stable supply, and while the mega-pharma subsidiaries may undertake development of vaccines the megas themselves have little interest in developing medical devices and are unlikely to develop microneedles. MEDRx then drew up a detailed plan for mass production and, in order to expedite discussions with some of the major pharmaceutical companies, decided to build a high-volume plant. In April 2018, it announced a capital raising plan for this purpose. In November, however, the fund raising ran into difficulties and MEDRx shelved the plan to build a high-volume plant.

But the key to the vaccine business is the existence of a high volume production facility, and this means raising the necessary funds

However, in 2019, there arose the possibility of milestone income from development of tizanidine tape and it was decided to allocate this income, not to a high-volume factory, but to a clinical trial facility, with a start-up date of April 2020. With this, the company became able to produce to GMP-standard drugs for administration to human subjects in clinical trials.

As a result of discussions with a possible tie-up partner it was dcided the clinical trial faciliy would be expanded to handle proliferative viruses and genetically modified organisms.

Later, in July 2020, the company held discussions on feasibility studies with several domestic makers and, in order to move closer to a corporate tie-up, decided to upgrade the facility to one which could handle pathological bacteria and viruses used in vaccines, along with genetically modified organisms. At the same time, the company announced a capital raising exercise to finance this. This was to consist of a third party allotment of new shares and the issue of warrants (No.17) on new shares (the total capital raised was JPY1.118 billion, of which JPY480 million was for microneedles. Warrant exercise was completed on January 12 2021 (amount raised: JPY735 million). An upgrade to the test facility to handle pathological bacteria and viruses used in vaccines, along with genetically modified organisms, was completed on January 28, 2021 with the emphasis

centering on "diffusion prevention and other biosafety measures".

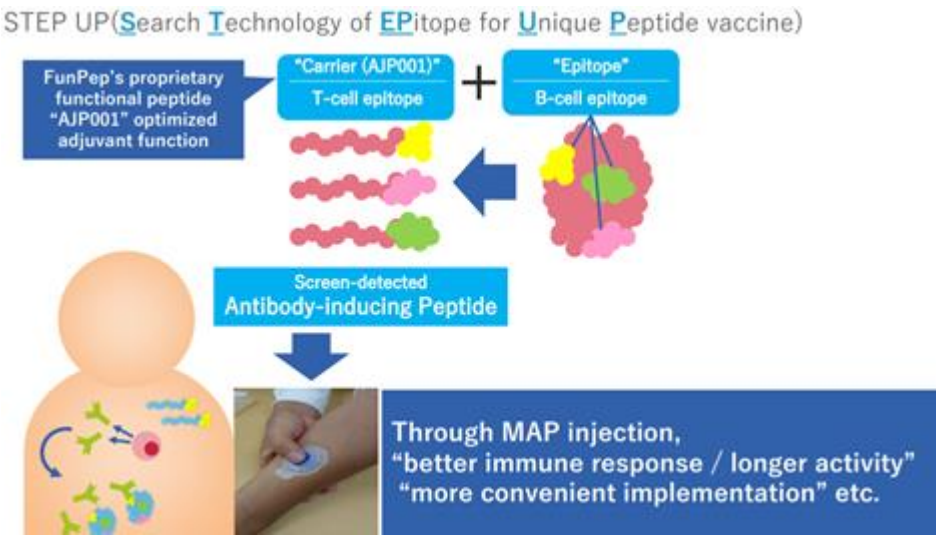
Feasibility studies are now being undertaken with a number of pharmaceutical companies and vaccine ventures

At present 5-10 domestic and foreign pharmaceutical companies and vaccine ventures are carrying out feasibility studies (tests on animals) before deciding on an operational tie-up. In August 2021 it was revealed that a feasibility study had been conducted on a formulation in which FunPep's antibody-inducing peptide (AJP001) was applied to MEDRx microneedles. Peptides are cheaper than antibodies and their use could help reduce cost. By administering a peptide that produces the targeted antibody with a microneedle, long-term antibody production is possible and convenience is improved.

Long-term antbody production possible with microneedles

The FunPep antibody-inducing peptide and microneedle formulation

The results of tests on human subjects is key to attracting the interest of the mega-pharmas



Source: MEDRx company briefing, August 2021

It may be possible in 2023 to move beyond animal studies to the next stage (tests on human subjects). This will continue to be well worth watching

2021 results and 2022outlook

In 2021 the milestone income from Cipla was delayed and there was no milestone income from DWTI. But the development costs of lidocaine tape peaked out and losses contracted

Sales in 2021 totaled only JPY8 million and this came entirely from sales of Iodine ointment. A USD2 million milestone payment for 2020 expected from Cipla related to tizanidine development was deferred until 2022 due to the delayed start of Phase-2, and a JPY100 million payment for development cooperation from DWTI did not materialise on failure of Lydolyte to get approved. On the other hand, mainly because of the peak-out in Lydolyte, development R&D expenditures fell JPY160 million from the previous year to JPY794 million. This shrinkage in R&D helped reduce the deficit to just over JPY1 billion at the operating level and around the same at the net level.

In 2022 the company expects milestone income from Cipla to boost sales, but growth in R&D expenses should keep losses at around the same level as 2021

In 2022, sales are expected to rise significantly to JPY289 million. This will consist of a JPY9 million contribution from iodine ointment sales, a Cipla milestone payment of some JPY220 million, and multi-million yen contributions from progress in other areas. In addition, Lydolyte authorisation is likely to happen in 2023, meaning the development cooperation payment of JPY100 million from DWTI will not materialise in 2022. R&D expenditures are likely to exceed JPY1 billion, about JPY290 million above the 2021 level. This is due to a number of expenditures, such as those required for Lydolyte supplementary tests and the submission of a new application, for the start of memantine clinical trials, and for fentanyl development. As a result, notwithstanding the increase in sales, and while non-R&D management costs will be reduced, it is likely that operating profits will record a loss of just over JPY1 billion, around the level of the previous year. Net income is likely to come in at just over JPY1 billion, again on a par with the previous year.

2021 results and 2022 outlook

(JPY-mil)

	2012/12	2013/12	2014/12	2015/12	2016/12	2017/12	2018/12	2019/12	2020/12	2021/12	2022/12 (company est.)
Sales	87	68	26	37	22	198	8	169	115	8	289
Goods Sold	71	33	26	37	22	28	8	23	15	8	9
R&D Income	16	36	0	0	0	170	0	146	100	0	280
Cost of Sales	33	8	9	12	8	7	2	5	4	2	2
SG&A	621	664	1,020	1,025	1,357	1,174	1,279	1,792	1,241	1,067	1,289
R&D	415	397	718	716	1,074	888	980	1,512	967	794	1,085
Other Admin.	206	267	302	309	283	286	299	280	274	273	203
Op. Income	-567	-604	-1,003	-999	-1,342	-983	-1,273	-1,627	-1,130	-1,061	-1,002
Rec. Profit	-578	-616	-1,012	-990	-1,301	-988	-1,285	-1,633	-1,152	-1,074	-1,003
Net Income	-571	-621	-1,016	-878	-1,259	-884	-1,267	-1,616	-1,114	-1,059	-1,006

Source: Fair Research Inc. using materials from the MEDRx results meeting

At the end of 2021 the sompany had cash of around JPY1.7 billion on the balance sheet, some 18 months of requirements

Cash on the balance sheet at the end of December 2021 stood at JPY1.73 billion, equivalent to 18 months of forecast 2022 net income. In 2021, MEDRx raised JPY865 million with the exercise of its series 17 new share warrants, and the issue and exercise of series 20 and series 21 (completion of series 17 rights in January 2021, of series 20 in August 2021, and of series 21 in December 2021). Elsewhere, there was a JPY50 million repayment of short-term borrowings (reducing fixed liabilities), such that cash flow from financing activities came to a positive JPY815 million. Operational cash flow recorded a negative JPY923 million, reflecting shrinkage in net losses. Cash on the balance sheet fell by JPY110 million.

Lydolyte supplementaries and re-submission now on the cards

Early deveopment work on diclofenac-lidocaine tape deferred beyond the original plan

The amount raised from the issue and exercise of series 20 warrants was JPY555 million, and from series 21 JPY248 million, for a total of JPY793 million excluding administrative charges. This was scheduled for allocation to finance animal tests related to the microneedle pipeline (JPY285 million), initial development of diclofenac-lidocaine tape (JPY421 million) and the costs of preparing for Phase-2 of tizanidine tape (JPY87 million). After completing supplementary Lydolyte tests a re-submission of the application is necessary and there was therefore a change in the uses of funds scheme (February 2022), with the allocation to initial development of the diclofenac-lidocaine tape being reduced to JPY7 million. The difference was transferred to Lydolyte supplementary test costs and the cost of re-submitting an application, and also to supplement running costs up to July 2022.

Balance sheet

(JPY-mil)

	2012/12	2013/12 IPO	2014/12	2015/12	2016/12 CB issued	2017/12 CB converted	2018/12	2019/12	2020/12	2021/12
Liquid Assets	507	4,008	2,857	2,204	2,736	1,836	1,937	1,501	1,886	1,754
Cash	465	3,937	2,780	2,063	2,640	1,737	1,796	1,410	1,812	1,703
Others	42	71	77	141	96	98	141	91	74	51
Fixed Assets	280	722	831	774	342	296	373	546	410	353
Tangibles	215	256	346	278	264	220	295	471	328	270
Intangibles	0	1	3	2	1	0	0	0	0	0
Investments e	65	465	483	494	76	75	77	75	82	83
Total Assets	787	4,730	3,685	2,978	3,079	2,133	2,311	2,047	2,297	2,108
Liabilities	511	227	171	205	573	99	180	126	149	153
Current Liabs	450	158	79	110	103	88	170	116	122	125
Fixed Liabs	61	69	92	96	469	10	10	10	27	27
Net Assets	275	4,503	3,514	2,772	2,507	2,037	2,130	1,920	2,147	1,955

Source: Fair Research using company's short-form results filings

Changes in uses of funds and timing of expenditures (from series 20/ 21 new share warrant exercise)

（Original）

Uses of funds	Millon Yen	Period of spending
①Animal studies to examine the feasibility of MN products such as vaccines for infectious diseases	285	2021June～2022May
②MRX-6LDT:Initial development of chronic pain treatment	421	2021June～2023March
③CPN-101（MRX-4TZT）Costs of tizanidine tape Phase-2 prep.	87	2021Sep.～2022April
Total	793	

（Revised）

Uses of funds	Millon Yen	Period of spending
①Animal studies to examine the feasibility of MN products such as vaccines for infectious diseases	285	2021June～2022May
②MRX-6LDT:Initial development of chronic pain treatment	7	2021June～2021Dec.
③CPN-101（MRX-4TZT）Costs of tizanidine tape Phase-2 prep.	87	2021Sep.～2022April
④Costs of extra tests for MRX-5LBT and re-submission of application	158	2022Feb.～2022Dec.
⑤Operating capital	256	2022Feb.～2022July
Total	793	

Source: MEDRx Timely Disclosure documents, Feb. 10, 2022

We have re-calculated the pipeline value taking into account changes in the market and changes in development status

Reference: Pipeline current value calculation

On the basis of the foregoing, Fair Research Inc. has recalculated the current value of the pipelines using the discount cash flow (DCF) methodology.

Note: In the final analysis, this is an estimate based on some challenging assumptions and should be seen as only indicative.

Preliminary assumptions behind calculation

We see it taking about 4 to 5 years from product launch to peak sales, after which sales will decrease at an annual rate of 5% until 2040, from which point the development of generics will push sales down 10% annually in what we see as the product's final stage.

The discount rate is set at a relatively high 12%, this being the 8% ROE required by investors and reflecting the fact that MEDRx does not yet have a major product in the market, is operating at a loss and is viewed as a bio-venture. Royalties income will depend on the development stage at which licensing-out occurs but we have provisionally set this at 10-15% of sales. Pipeline milestones are generally posited at one-quarter of peak sales, with the exception of tizanidine tape for which the actual numbers have been released.

In the case of tizanidine tape, delays in develoment have led to retarded entry into the market

(1) Tizanidine Tape（MRX-4TZT, CPN-101）

We are assuming that preparations for Phase-2 will be the responsibility of MEDRx, following which the sub-licensee will be responsible for promoting development. Milestone payments should be in line with the current contract. As for the future development schedule, we are assuming in our estimate that Phase-2 will be undertaken in 2022-2023 and that Phase-3 will start in 2024. We are further assuming that a new drug application will be submitted in 2026 and that market launch will be approved in 2027. We are assuming peak sales at around 30% of current sales of muscle relaxant, or JPY30 billion. Additionally, since licensing-out occurred at the completion of Phase-1, royalties are posited at a low 10%, and since the product's current development status is pre-Phase-2 we posit probability of success at 50%.

We are positing a conservative estimate of peak sales and milestones in light of the experience of ZTlido®, a forerunner of tizanidine tape

(2) Lidocaine Tape（Lydolyte；MRX-5LBT）

For lidocaine tape (Lydolyte) our schedule posits re-submission of an NDA in the second half of 2022 and authorisation/licensing-out in 2023. Market launch we assume will be in 2024. For sales we are assuming Lydolyte will, at peak sales, capture a market share of 10%, or 12.9 million tapes (2020 sales of lidocaine tapes 129 million). We have assumed a competitive price of $3 per tape, compared to $4-5 per tape for ZTlido®, and 1.5 times the price of conventional generic products in consideration of differentiating characteristics. This works out at revenue of around JPY4.4 billion at peak sales. Along with this, the milestones associated with the licensing-out have been set at JPY1.2 billion, which is about a quarter of peak sales. The market environment is very competitive but, because the licensing-out will be at or around the time of regulatory approval, we have set the royalties rate at 15%.

As the application for approval has already been accepted we posit probability of success at 100%. And the profit distribution with DWTI is assumed to be 9:1.

(3) Memantine（MRX-7MLL）

Looking ahead, Phase-1 is about to start, and Pivotal BE trials and long term stability tests will be completed in 2023. We anticipate an application for approval in 2024, authorisation in 2025 and market launch in 2026.

- Since the product has cleared pre-clinicals and Phase-2 and Phase-3 are not required we posit probability of success at 60%.
- With a market share at peak sales of around 25%, and assuming the same price level as preceding products, we posit revenues of JPY18.8 billion.
- We have set royalties at 12% and milestones at JPY5 billion.

(4) Fentanyl tape（MRX-9FLT）

The fentanyl transdermal market consists almost entirely of generics. The MEDRx product offers a mechanism to prevent accidental misuse, and the appeal of this feature could secure it a market share of 50%. The product has new features, but given the competition we are assuming a price level about 1.5 times that of existing generic products.

We posit a launch date for fentanyl tape of 2025 and peak sales revenues of JPY15.7 billion

- Since the fentanyl transdermal market in 2020 was valued at JPY21 billion (MEDRx company briefing) we are assuming peak sales of JPY15.7 billion
- We are positing an NDA and a licensing-out in the second half of 2024, followed by receipt of approval and market launch in 2025. Looking ahead the only requirements prior to making an application are bio-equivalence tests and accidental misuse prevention tests. Thus, we posit an 80% probability of success.
- We have assumed the royalties will be 15%. Milestones are set at around a quarter of peak sales, or JPY3 billion.

(5) Diclofenac-lidocaine tape (MRX-6LDT)

Blockbuster-level sales are expected for diclofenac-lidocaine tape

- An estimated 9 million patients are receiving treatment for knee osteoarthritis (Knee-OA) in the US. In addition, the market for NSAIDs for such sufferers is estimated at JPY440 billion (please see our Sept. 2021 report “Next Major Product Has Blockbuster Potential)”.
- We assume a price of USD10 per tape, with patients being prescribed one tape per day.
- Assuming 3% of the 9 million patients use diclofenac-lidocaine daily, the total amount comes to USD980 million, for a peak market value of JPY100 billion, or one-quarter of the NSAIDs market.
- We assume licensing-out will occur in 2026 simultaneously with the completion of Phase-2, and that the licensee will handle Phase-3 and beyond. We further assume an NDA will be submitted in or around 2029 and that approval and market launch will occur in 2030.
- Since the tape is still at the pre-clinical stage we estimate a 20% probability of success, somewhat lower than other pipelines.

Further, we posit a potential market for microneedles (vaccination-use alone) of between JPY50 billion and JPY1 trillion (MEDRx company briefing materials, February 2021). However, since the scheme for commercialisation has not yet been clarified we omit this product from the calculation.

While we estimate a sizeable potential market for microneedles we are omtting it from the current calculation

Assumed development and commercialisation schedule (summary)

	Status	2022	2023	2024	2025	2026	2027	2028	2029	2030
MRX-4TZT	Phase-1 completed Prep for Phase-2	Sub-license tie-up Start of Phase-2	Ph2	Ph3	Ph3	Ph3＋NDA	Approval/launch			
MRX-5LBT	Discusaing with FDA further tests	NDA in second half	Approval Licensing-out (sales)	Launch						
MRX-7MLL	Transfer of prod. technology IND submitted	PK	BE test Long stability Test etc	NDA Licensing-out (sales)	Approval	Launch				
MRX-9FLT	Fast Track status Pilot PK finished	Pivotal BE	Accidental misuse prevention	NDA Licensing-out (sales)	Approval/launch					
MRX-6LDT	Formulation development	Pre-cilinical	Ph1a	Ph1b,c	Ph2	Ph2 Licensing out (dev., sales)	Ph3	Ph3	Ph3＋NDA	Appproval /Launch

Source: Compiled by Fair Research Inc.

Note: The above is a best case scenario, but it should be borne in mind that delays and suspensions are possible

Sales targets set (summary)

	Market value of indications	Market share (approx)	Price assumptions	Sales target (JPY100 mil)
MRX-4TZT	Muscle relaxant (US) JPY110bil	30%		300
MRX-5LBT	Lidocaine patches.129 million. Net market value JPY27 bil.	10%	Net basis USD 3 each （Zlido: USD 4-5）	44
MRX-7MLL	Oral memantine Mostly generiics:J JPY12 bil. Before generics: JPY75 bil	25%	Around same as predecessors	188
MRX-9FLT	Fentanl tape （Mostly generics） JPY21 bil	50%	1.5X generics	157
MRX-6LDT	Knee OA 9 mil. patients (NSAIDs JPY440 bil）	3%	Once daily USD10/patch	1,000

Source: Fair Research Inc.

Results of trial calculation

As a result of conservative assumptions, particularly with respect to competition with generics, we arrive at a current value for the five pipelines of JPY27.6 billion (before taxes and after taking the probability of success into account). Setting a 100% probability of success for all pipelines would yield a value of JPY68 billion (before taxes). The success probability of diclofenac-lidocaine tape greatly affects the estimated value. As pipeline development progresses so does the probability of success and with it pipeline value. At the present time the market is valuing MEDRx's market value at around JPY2.7 billon, quite a long way from the five-pipeline pre-tax present value even given our fairly conservative assumptions. Quite possibly, with Lydolyte's re-submission, and with delays in the development of other pipelines, the market is finding it difficult to accurately estimate the value of the pipelines.

We calculate the present value of the five pipelines at JPY27.6 billion

Due to delays in development and bringing product to market the calculation of pipeline value is not an easy task

Discounted Present Value of Pipelines (before tax)

(JPY100 mil)

	Before prob of success	After prob of success
Lidocaine tape （MRX-5 LBT） Prob of success 100%	37	37
(Excl. contrib. from DWTI)	33	33
Fentanyl tape （MRX-9 FLT） Fast track 80% prob of success	108	85
Memantine transdermal （MRX-7 MLL） 60% prob of success	93	51
Tizanidine tape （MRX-4 TZT） 50% prob of success	96	48
Diclofenac-lidocaine tape （MRX-6 LDT） 20% prob of success	350	60
sub-total	684	280
Excl DWTI contrib	**680**	**276**

Source: :Estimates by Fair Research inc

Note: Estimates may vary depending on assumptions

Corporate value determined not only by pipeline value but by various costs and tax, etc.

Lidocaine tape will provide steady income while other develoment products move closer to the market stage. This could possibly mean the company turning profiable

If the results of miconeedle tests on human subjects lead to a partnership with a pharmaceutical major, this could boost the company's value very quickly

If Lydolyte lidocaine tape is successfully licensed out and launched, it could provide MEDRx with a stable source of income. Subsequent to the launch of Lydolyte in 2024 a series of products will make an appearance in the market, including fentanyl tape (around 2025), memantine patches (around 2026), and tizanidine tape (around 2027). In addition, some time around 2026 there could be a licensing-out of diclofenac-lidocaine tape, expected to have blockbuster sales potential and boosting MEDRx's status to the next growth stage. Finally, if microneedle vaccines are successful in first-in-human studies (possibly as early as 2023), this could attract a lot of attention from the major pharmas and, with the acquisition of the funds required for mass production, could give MEDRx an entirely different rating in the market.

Conclusions

2021 was a stagnant year for MEDRx, particularly in the following three areas:

① MEDRx envisaged that Lydolyte lidocaine tape would emerge as its first product to market. In fact, however, it failed to gain approval and was required to undergo further testing and a re-submission of application for approval. This meant the milestone income of JPY100 million it was scheduled to receive at the time of approval did not materialise.

② The task continued of selecting a sub-licensee for tizanidine tape (CPN-101; MRX-4TZT), which had been licensed out to Cipla, delaying the start of Phase-2 and the receipt of a JPY220 million milestone payment.

③ The plan was to start Phase-1 pre-clinicals for memantine patches in 2021 but the COVID-19 pandemic held back the selection of an investigational drug producer and the transfer off technology. Phase-1 is now due to start in 2022 (investigational trial application 2021).

Behind the scenes, however, the company has been working on some major development possibilities. In August 2021 the company announced it was starting development of diclofenac-lidocaine tape (MRX-6LDT), for which it has high hopes in the market. However, in 2022, development funds were switched to cover the costs of supplementary tests for Lydolyte, so MRX-6LDT remains at the pre-clinical stage. Phase-1 has been put off until 2023 or later. The plan now is to complete Phase-2.

Nevertheless, the plan now is to complete Phase-2 and license out in around 2026, when first movers will have started to develop the market. Also, fentanyl tape (MRX-9FLT) received fast track status from the FDA in July 2021and it is moving towards Pivotal comparative tests of bioequivalence with the reference product, Duragesic®. Further, in the high-potential area of microneedles an upgrade to the test facility was completed in January 2021, focusing on bio-safety measures for the prevention of proliferation and thereby allowing the handling of pathogenic bacteria, viruses and genetically modified organisms. At present, feasibility studies are being undertaken by pharmaceutical companies and vaccine ventures at home and abroad. MEDRx hopes to see strong interest from mega-pharmas if tests on human subjects in 2023 are successful.

Looking ahead, it is likely that, if development proceeds smoothly, a stream of new products will come to the market in 2024 and after. The company's value will benefit considerably when investors discount further development of diclofenac-lidocaine tape (MRX-6LDT) and microneedle "vaccine patches". At the moment, only Lydolyte lidocaine tape, expected to be the company's first to market, has been discounted in the company's market value of around JPY2 billion.

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