MEDRx (4586) TSE Mothers

Outstanding technology that can revolutionize the administration of vaccine

Yuya Okamura, Analyst

Company profile	
Location	Higashikagawa-shi, Kagawa
Representative	Yonehiro Matsumura
Established	January 2002
Capital	\7,679 million
Listing	February 2013
URL	http://www.medrx.co.jp/index.html
Sector	Medicine

Stock price data (closing price on September 16)	
Stock price	175
Outstanding shares	21,965,100shares
Trade unit	100shares
Market cap	\3.84billion
PER (est.)	-
EPS (est.)	-
PBR (actual)	99.60x

LA bio venture striving to enter the American market with adhesive skin patches – a product that has never seen in the U.S.

MEDRx is a venture company that was established in Higashi-Kagawa-shi, Kagawa in January, 2002. Capitalizing on 'ILTS', MEDRx's **proprietary technologies using ionic liquids, the company is engaged in development of adhesive skin patches.** The company has successfully passed the P1b trials and preparations are underway to implement the phase II trials by the end of 2021. MRX-5LBT, which is expected to be used as a therapeutic drug for post herpetic neuralgia, is the closest pipeline to sales. MEDRx concluded a joint development agreement with D Western Therapeutics Institute in April 2020. In October of the same year, the company's NDA was accepted by the U.S. FDA. Moving forward, MEDRx is advancing on a timeline of receiving approval in the second half of 2021 and bringing the product to market in 2022. The company is currently exploring sales partners in the U.S.

nMicroneedle, innovative medical device

In addition to being painless, they have advantages such as improving-immune effectiveness during vaccination and enabling transportation-/storage at ambient temperatures. Consequently, microneedles are attracting attention as a promising medical device in the future. In April 2020, MEDRx started operation of a microneedle factory for investigational drugs.

n Large room for reviewing the value of the company for its world-changing adhesive vaccine technology

The projection for the current term is net sales of 327 million yen, a negative balance in the ordinary income of 890 million yen, and a negative balance in net income of 1,117 million yen. The approval of MRX-5LBT as a new drug in the US and launch of phase II trials of CPN-101 are promising news in the pipeline in the second half. In addition, for non-adhesive skin patch pipelines, microneedles are anticipated to once again attract great attention. Compared to injectable vaccine products, microneedles generate a higher immune response, and in terms of vaccine dose, only 1/100th of the dose of a single injection is required for an equivalent injection effect. Furthermore, the applicator does not need to be frozen during transportation or storage, and moreover, self-administration can be performed. Therefore, microneedles can contribute greatly to the progress of vaccination in developing countries that lack proper healthcare environments and help eliminate the vaccine shortage problem. This outstanding technology is too exceptional to be unused, and the company behind the technology has the smallest market cap in bio ventures listed in the Mothers section. These facts indicate there is plenty of room to review its value.

Point summary（1）

●What kind of company is MEDRx?

MEDRx is a venture company established in January, 2002 in Higashi-Kagawa-shi, Kagawa. In February, 2013, the company was listed in the Tokyo Stock Exchange Mothers. Capitalizing on 'ILTS', MEDRx's proprietary technologies using ionic liquids, the company developed adhesive skin patches and is currently trying to create the topical/transdermal tape product for the U.S., country boasting an enormous market. Unlike other regular venture companies, MEDRx's aim is not to develop new APIs. MEDRx is a company, which is engaged in development of a new platform for APIs already used in a range of medicines for internal use or injection drugs, with the idea to use these APIs in adhesive skin patches or ointments. For that reason, although the company is expecting same high returns as a venture developing new APIs, the risks are on a much smaller level, so the business model of MEDRx is quite special.

●What are the special advantages of adhesive skin patches in the first place?

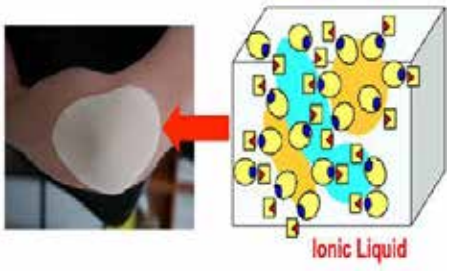
The best known kind of adhesive skin patch in Japan is surely the anti-inflammatory analgesic plaster. There are many kinds of drugs including oral medicine, injection drugs, ointments, etc., but the adhesive skin patches including anti-inflammatory analgesic plasters have four major advantages.

(1)The first is that the pharmacologically effective agent is released gradually. Because the medicine comes out slowly, it is easier to keep blood concentration constant and continuously maintain benefits of the drug.

(2)Because these drugs do not pass through the liver like orally taken medicines, the liver does not bear the burden of breaking them down. Side effects are rare.

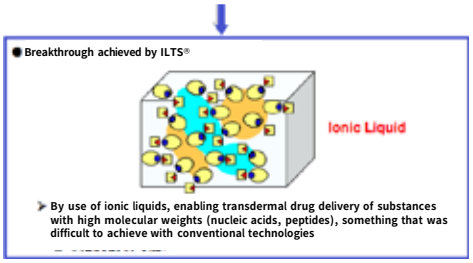
(3)Risk of forgetting to take medication can be eliminated. In case of overdosage, one can simply remove the patch. One can even apply the patches to the backs and other parts of the body of infants and young children where they won't be seen.

(4) There is no pain like with injected pharmaceuticals.



Limits of conventional transdermal drug delivery technology

- It is limited to the medicines with certain physico-chemical qualities (low molecular weights, oleophilic agents, and medicines with low melting points).



●What sort of technology is 'ILTS', the proprietary technology of MEDRx?

The skin serves as the first barrier protecting the human organism from invasion of foreign substances. For this reason, many of the drugs could not be efficiently delivered into the body using the conventional transdermal drug delivery technology. MEDRx pioneers the use of ionic liquids to create adhesive skin patches for drugs that could not previously be administered through such patches.

The key features of ionic liquid are its low melting point (100 degrees and below), that it remains liquid at room temperature, and that its (equilibrium) vapor pressure is virtually zero. Furthermore it is incombustible, and boasts excellent solubility. MEDRx is the first company in the world that took a technology, which was commercially exploited by other industries in such areas as lithium-ion and solar cells, and managed to use it for medication. The company has acquired medical patents for every pipeline, protecting high barriers to entry.

Point summary（2）

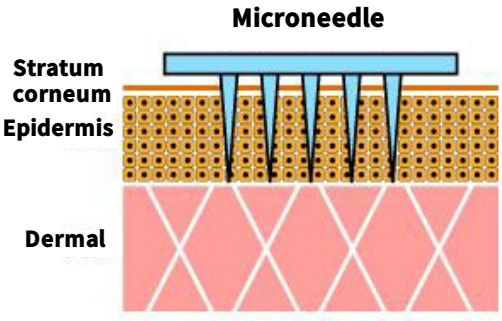


Image 1

Image 2

Image 3

- **What is a microneedle?**

A collection of tiny needles made of biodegradable resin is called a microneedle (MN). As shown in the figure on the left, the MN is inserted into the skin, but it has the advantage of being painless because it consists of tiny needles. MN is an advanced painless transdermal administration system that locally punctures the stratum corneum and administers vaccines and drugs to the dermal layer.

Currently, the development of a vaccine for COVID-19 is an urgent issues throughout the world. When administrating this vaccine, MN is expected to enhance the effect of immunity compared to conventional injection. Additionally, it has the merit of being expected to provide a faster effect than oral drugs. Consequently, MN is attracting attention as a promising administration device in the future.

- **Revolutionary vaccination device with high potential**

MN, which is subject to high expectations as a new medical device, has a potential market size of up to 1 trillion yen. In Japan, corporations such as Fujifilm and Nipro are also attempting to enter the MN market; however, no industry players have reached the stage of mass production as medical devices.

MEDRx has already begun operation of a therapeutic drug factory for MN, a device with high potential. The company's unique applicator (the Japan Patent Office made a decision for a patent grant in August 2020) is an extremely innovative device that reliably and easily inserts MN into the skin. The applicator is the size of a business card or smaller (back of device shown in Image 1; front shown in Image 2) and it is lightweight. Multiple applicators can be placed in an envelope for mailing.

This would enable vaccines to be distributed to all households, even in the event of an infectious disease pandemic. The applicator does not need to be frozen during transportation or use. Moreover, once delivered, the applicator has an advantage over conventional injections because self-administration can be easily performed by anyone upon delivery. Moreover, the applicator has an advantage over conventional injections because self-administration can be easily performed by anyone upon delivery. The MN patch is attached simply by placing the applicator holding the MN on your arm and pressing it vertically (Image 3).

This innovative medical device is expected to achieve outstanding performance after being commercialized and put into mass production. This performance will be achieved in terms of protecting the medical system in the event of a pandemic and contributing to emerging countries where the medical environment is not well established.

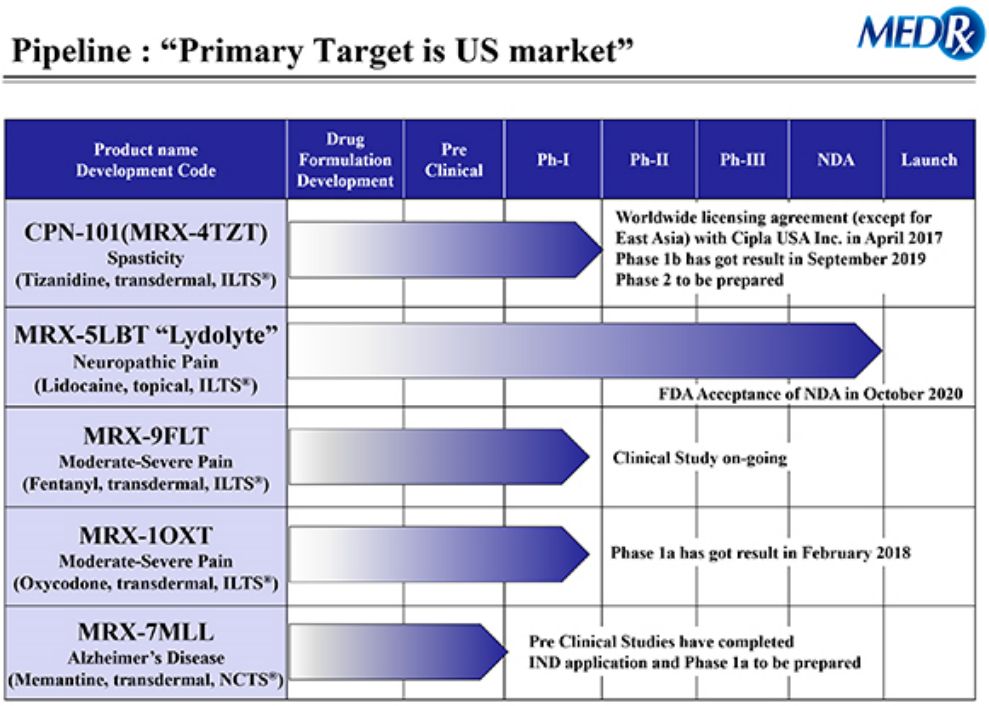
Development pipeline: present conditions and prospects (1)

① 「CPN - 101」 (「MRX-4TZT」)

An adhesive skin patch containing tizanidine, a centrally acting muscle relaxant that is used in Japan to treat a number of symptoms including stiffness of the shoulders. The size of the US market for neuromuscular junction blocking drugs is huge: approximately 110 billion yen (partial estimate in 2020). Oral tizanidine medication requires 3 doses per day, and there are also side effects such as liver dysfunction and drowsiness. If made into an adhesive skin patch, one needs to apply the patch only once during the day and the medicine will be effective throughout the day slowly entering the body and keeping the blood concentration on the same effective level.

Phase I of clinical trials for MRX-4TZT was completed in February 2017, and the results were favorable. The same level of blood concentration as with medicine for internal use containing tizanidine currently on the market was confirmed, and there was almost a complete absence of side effects such as drowsiness. Also, this April, the company signed a global (with the exception of East Asia) development and sales licensing contract with Cipla USA, the American 100% subsidiary of Cipla, a major pharmaceuticals company in India. In addition to the lump sum payment for executing this contract, this large-scale contract features favorable conditions such as a maximum of 30 million USD (about 3.3 billon yen) provided for milestones in development and sales progress and graduated royalty income for sales after products enter the market.

The added phase I clinical trials (P1a'), which were started in September 2017, yielded favorable results in January 2018, meeting the standards which had been determined in cooperation with Cipla beforehand. The next challenge is the P1b trials, MEDRx had to manufacture an investigational new drug in the form scaled up to the commercial production level, and conduct, using the investigational new drug, the same repeated dose trials as were done during P1a'. In September 2019, MEDRx was judged to have achieved good results that satisfied the criteria determined beforehand. Preparations are ongoing under the leadership of Cipla to move onto the subsequent phase II trials by the end of 2021.



Development pipeline: present conditions and prospects (2)

② 「MRX-5LBT」 “Lydolyte”

An adhesive skin patch with lidocain, a local analgesic. The product is developed to be used as a therapeutic drug for neural pain. The US market of lidocaine patches is about 27 billion yen (partial estimate in 2020). In June 2018, confirmatory comparative clinical trials demonstrated the biological equivalence of MRX-5LBT with Lidoderm, a drug that had scored a major hit in the target U.S. market (bringing in annual sales of over 100 billion yen at the peak). MEDRx’s product showed the competitive advantage of expecting the same efficacy with just a little amount of lidocaine. Subsequently, the company implemented all clinical trials necessary to submit a new-drug application (hereinafter: NDA) as required by the U.S. FDA. In August of the same year, as initially planned, the company filed a new-drug application (NDA) with the FDA in the US. The company has been notified of the completion of the review process by the FDA, and MRX-5LBT “Lydolyte” is expected to receive approval within 2021 without additional trials when appropriate action is taken for items noted by the FDA. There are no changes planned for the most optimal schedule based on the assumption that the product enters the market in 2022.

③ 「MRX-9FLT」

MRX-9FLT is an adhesive skin patch containing fentanyl, a designated medical opioid. The US market of fentanyl patches is about 21 billion yen (partial estimate in 2020). Since becoming available about 20 years ago, Fentanyl patches have been used in the U.S. to relieve severe acute pain, chronic pain, and cancer pain. Although the company is not a pioneer in this area, there have been many reports of fatal accidents involving infants and children caused by misuses of the existing patches. This new pipeline was established by MEDRx to ensure that such accidents do not happen again. If the company succeeds in adding value by using its proprietary technology to prevent such misuse-induced accidents, such innovation may help MEDRx to increase its market share. At a meeting with the company in May 2019, the FDA identified this feature as an important and valuable goal. Precedence suggests that the probability of approval is high. The lowered costs in association with less testing should restrain the cost of development. On July 28, 2020, the company announced that clinical trials in the U.S. have started. MEDRx started clinical trials in the U.S. from July 2020. The company announced the first results of clinical trials in September 2020, confirming effects such as changes in blood concentration similar to that of the reference product (Duragsic). MRX-9FLT is designated as a fast track drug (designation for new drugs for expedited review) by the FDA in July 2021.

④ 「MRX-6LDT」

MRX-6LDT is an adhesive skin patch utilizing a high percutaneous penetration property to realize simultaneous administration of two drugs, namely, the anti-inflammatory drug diclofenac (pharmaceutical which has been sold for many years as prescription drug under the product name of Voltaren in Japan) and the local anesthesia lidocaine. This adhesive skin patch features the simultaneous synergistic effect of diclofenac and lidocaine, and it is expected to be used as drug for chronic pain. The size of the US market for chronic pain treatment drugs is huge: approximately 3.5 trillion yen (partial estimate in 2019). Hisamitsu Pharmaceutical Co., Inc. is also developing an anti-inflammatory drug adhesive skin patch that enables only diclofenac to be delivered in high concentration for the US market (launch of Phase III trials from January 2021). MEDRx plans to start non-clinical trials in the middle of 2021 and begin Phase I trials in 2022.

Results of Operations

Performance (million yen, %)

Fiscal year end	Net sales	YoY	Ordinary income	YoY	Net income	YoY	EPS(\)
December 2016	22	-40%	-1301	-	-1259	-	-
December 2017	198	787%	-988	-	-884	-	-
December 2018	8	-96%	-1285	-	-1267	-	-
December 2019	169	1923%	-1633	-	-1616	-	-
December 2020	115	-32%	-1152	-	-1114	-	-
December 2021 (est.)	327	184%	-1115	-	-1117	-	-

●During the first half of the term ending December 2021, the company posted net sales of 7 million yen, a negative balance in the ordinary income of 483 million yen, and a negative balance in net income of 473 million yen. Since the company focuses on formulation development, sales up until the second quarter when milestone income is not recorded will be nearly zero (sales solely from Iodocoat Ointment). Sales and general administrative expenses were 477 million yen, down from 717 million yen in the same period of the previous term since the schedule of implementation of clinical trials was changed from the initial plan. Compared to the same period of the previous term, losses also decreased.

Due to funds procured by exercising stock acquisition rights, the cash balance as of June 30, 2021 was 2,252 million yen, which was an increase of about 440 million yen from the end of the previous term. Two clinical trials a year (about 1 billion yen a year) have secured cash-on-hand for approximately two years.

●The projection for the term ending December 31, 2021 is net sales of 327 million yen, a negative balance in the ordinary income of 1,115 million yen, and a negative balance in net income of 1,117 million yen. The estimated net sales are based on development milestone income from CPN-101 and the milestone income from DWTI, with whom the company signed the MRX-5LBT joint development agreement (Total is 320 million yen). Sales and general administrative expenses are assumed to be 1,436 million yen.

Note: There was a possibility of the company's net sales in the term ending December 2021 falling under the stock delisting criterion of the Mothers section for net sales (yearly net sales of 100 million yen or more). However, it does not constitute a hindrance to the company's transition to the new Growth Market segment in market restructuring of the Tokyo Stock Exchange and concerns over delisting due to the net sales level have been eliminated.

Results of Operations

●In the Mothers section, the market caps of MEDRx and seven other listed bio ventures are less than 10 billion yen. The average performance of these eight bio ventures since the beginning of the year is -7.3%. Performance pales significantly in comparison to the US NASDAQ biotechnology index since the start of the year, which is 12.1%. However, the only reason for this difference must be the listing in a different market. Although the release of quarterly performance results is mandatory, presenting changes every three month is difficult for bio ventures that are working on research and development of new API development pipelines. However, on the Tokyo Stock Exchange, most trades are by individual investors trading in stocks in a short period of time (plus margin trading), therefore, announcements of quarterly performance are major events, and it is unavoidable that such quarterly performance announcements offer opportunities for individual investors to make trading decisions. The stock price premium granted to the growth potential of bio ventures is small compared to the US market since, in the US market, operating funds of the Growth Stock Fund are quite enormous and the ratio of stocks that are held by investors in the long term is high.

Bio ventures listed in Tokyo Stock Exchange face this dilemma. Since few small- to medium-size funds include bio ventures that are in deficit in their portfolios, the ratio of individual investors among active investors becomes relatively high. In the case of MEDRx as well, the outstanding balance of margin buying is 2,422,400 shares as of September 10, 2021, which accounts for as much as 11% of the number of issued shares.

The stock price is in its lowest price range since the beginning of the year, and the outstanding balance of margin buying acts as pressure for selling on rally. When looking at volume by price range for the past six months in consideration of the date of margin transaction, the price range where trades are made most is 250 yen and followed by the 225-yen range. Over time, supply and demand adjustments progress, but pressure for selling on rally is considered to be stronger in the 225 yen and higher range.

●Bio ventures listed in Tokyo Stock Exchange are susceptible to trading by individual investors, however, the company has the potential of attracting interest for different factors than just bio ventures. Separately from the pipeline for the adhesive skin patch, the company has been working on research and development of microneedles. Some media outlets have reported that microneedles are an injection patch that is applied to the skin, and as a result, the company was able to create an opportunity to significantly increase its trading volume. This is a result of the interest in microneedles as an innovative device in administration of the COVID-19 vaccine.

In US and European countries where more people are already vaccinated with the second dose, the administration of a third dose has already begun. On the other hand, developing countries, where vaccinations are behind, are facing shortages of vaccine. Thus, the microneedle can also contribute to resolving this problem. Compared to injectable products of vaccine, microneedles generate a higher immune response, and in terms of the dose of vaccines (antigens), it is said that only 1/100th of the dose of a single injection is required for an equivalent injection effect. This is not the only advantage of the microneedle. Additionally, the applicator does not need to be frozen during transportation or storage (The microneedles enable the transportation at ambient temperatures). Moreover, self-administration can be performed. Therefore, microneedles can contribute greatly to the progress of vaccination in developing countries that lack proper healthcare environments.

Many mid-cap and small-cap stocks were revaluated for COVID-19 related materials such as vaccine injection syringes, rapid antibody test kits, and power units for the storage of vaccine, etc. For microneedles as well, the company is currently looking for business alliances while carrying out feasibility studies (studies for the examination of feasibility) with pharmaceutical companies inside and outside of Japan and vaccine ventures . If microneedles can be established as medical devices for any drug without being limited to use for vaccine antigens, microneedles can change society. This technology is too outstanding to be unused, and it is expected it will become visible to investors. The market cap of the company (3.84 billion yen as of September 16) is the smallest even among bio ventures listed in the Mothers section. As soon as any sort of catalyst appears, the market impact at that time will inevitably be tremendous. (Okamura)

Stock Price (historical)	
Year high	\471
Year low	\150
Highest since the IPO	\7,500
Lowest since the IPO	\150

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