

MEDRx (4586)

TSE Mothers

Providing safety and stability in the US pain management market

Yuya Okamura, Analyst

Company profile

Location	Higashikagawa-shi, Kagawa
Representative	Yonehiro Matsumura
Established	January 2002
Capital	¥5,101 million
Listing	February 2013
URL	http://www.medrx.co.jp/index.html
Sector	Medicine

Stock price data (closing price on February 14)

Stock price	¥1,441
Outstanding shares	8,889,700 shares
Trade unit	100shares
Market cap	¥12.8billion
PER (est.)	-
EPS (est.)	-
PBR (actual)	6.58x

■ A 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. In April 2017, a global development and sales licensing contract was executed with Cipla, a major pharmaceuticals company in India, for 'MRX-4TZZT,' an adhesive skin patch which contains tizanidine, a centrally acting muscle relaxant. Added phase I clinical trials were started in September of last year, and favorable results that fulfill the prescript criteria were achieved in January of this year. In phase I of clinical trials for the 'MRX-10XT' adhesive skin patch, which contains oxycodone, this product also achieved favorable results in February of this year. There was a high probability of achieving the appropriate blood concentration of the drug and no side effects worthy of special mention were observed. There are a number of promising pipelines, and each of them is progressing smoothly.

■ Drastic sales increase through milestone MRX-4TZZT income

For the December 2018 period, anticipated net sales are 698 million yen (an increase of 252% over the previous period), with a passive balance in the ordinary profit and loss of 1,115 million yen (increased passive balance), and a passive balance in net earnings of 1,100 million yen (increased passive balance). A drastic sales increase is anticipated with milestone income from MRX-4TZZT as a prerequisite. Uncertainty remains regarding contract lump sum payments related to MRX-10XT and MRX-5LBT, so these are not included in the earnings forecast. Passive balances are increased due to the higher level set for research and development expenses compared to the previous period (1,562 million yen). This increase in research and development expenses is related to the smooth progress of pipelines, so it is natural to interpret this increase in passive balances in a positive way.

■ Pipelines progressing smoothly, silently moving to the next stage

Good news such as the favorable results of the MRX-4TZZT and MRX-10XT continues to be reported. Stocks have also risen tremendously since the start of 2018, reaching 1,753 yen for the first time this year on February 5th. However, the transaction volume on the same day was 4.2 million shares, which is high compared to the average daily volume last year of 452,000 shares. There was a correction from the high price as a result of the deterioration of Mothers, and it seems like a change in day-to-day market activity will be required to reach a yearly high for some time. At this point, when the contract party for the MRX-10XT license is determined, this will be big news. Just as with the cooperation with Cipla in April of last year, it will probably result in a strong buying impact for stock prices. Although stock prices fluctuate due to supply and demand alone, these fluctuations are not cause for rejoicing. Instead, we hope that the company will provide these new drugs as a safe and stable alternative to the opioids which are causing abuse problems in the United States and save the people affected.

Point summary (1)



● What kind of company is MEDRx?

MEDRx is a venture company established in January, 2002 in Higashi-Kagawashi, Kagawa. Masayoshi Matsumura, the founder and the current Chairman of the company, served as vice president at the Teikoku Seiyaku Co., Ltd. until 2000. Capitalizing on 'ILTS', MEDRx's proprietary technologies using ionic liquids, the company developed a number of 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. In February, 2013, the company was listed in the Tokyo Stock Exchange Mothers.

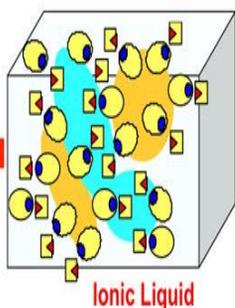
● What sort of technology is 'ILTS', the proprietary technology of MEDRx?

With the conventional percutaneous absorption technology, there are many drugs which do not easily penetrate through the skin. MEDRx is striving to utilize its technology using ionic liquid to pave the way for adhesive skin patches with drugs, which so far were not available for this kind of application. 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.

● 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 unlike orally taken medicines, these drugs do not pass through the liver, this organ 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.



Point summary (2)

● What are the attractions of the U.S., the intended market?

The U.S. people are said to be a 'population that is prone to pain'. The mainstay of the market of medicine for sharp pain in the U.S. is medicine for internal use, and the Americans use very strong analgesic drugs – morphine and other opioids.

The drug that holds the top share in this opioids market is oxycodone, a centrally acting analgesic drug. And MRX-1OXT is the pipeline, with which the company is trying to create a transdermal therapeutic drug blending its ILTS technology with oxycodone. In the U.S., the adhesive skin patch market has been already expanding since 2008 with products for mild to moderate pain.

The pioneer of this trend was 'Lidoderm' by Teikoku Seiyaku, for which the Chairman of MEDRx, Matsumura had served as vice president. 'Lidoderm' was quite successful after its release in 2000 and 'Flector', which was released after that, was also quite successful. The two together scored sales in the 100 billion yen per year range (both are hydrated type).

There is thus already a well-established track for selling adhesive skin patches in the U.S., and the market is starting to expand with new medicine also being developed for depression, ADHD, Parkinson, Alzheimer, and other diseases.



● Proprietary 'AMRTS' Technology: Striking down U.S. social problems

Opioids are the mainstream for pain relief medication in the United States, but opioid drugs like morphine and oxycodone are highly addictive and toxic. In spite of this, they are easy to get anywhere in the country as long as you have a doctor's prescription.

This structural issue has produced large numbers of opioid addicts, and it has become a social problem in the United States. Opioid abuse was the cause of 33,000 deaths in 2015. In October of last year, President Trump announced that he considered opioid abuse a problem and declared a public health emergency. This received a lot of attention in Japan as well.

Opioid abuse is a problem, and misuse when drugs are taken by mistake is as well. There have been cases of children who died after applying used opioid patches by mistake. Due to these social factors, the FDA has solidified its position and is not approving applications for new products without measures in place for preventing misuse.

In order to handle this FDA policy change, the company has researched technology for preventing abuse and misuse of opioid patch products. The result of these efforts is a proprietary new medicine technology called 'AMRTS.'

AMRTS is the combination of four different functional components: (1) low extraction (because the medicine is extracted slowly, it makes abuse difficult), (2) intense bitterness (even if a child accidentally puts a patch in their mouth, this bitterness ensures they won't swallow it), (3) re-absorption prevention (once the patches have been peeled off, almost none of the drug can be absorbed), (4) re-application prevention (once the patches have been peeled off, they are no longer very sticky and fall off easily).

Development pipeline: present conditions and prospects (1)

① 'MRX-4TZZ' (CPN-101)

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 88 billion yen as of the 2016 fiscal year. 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-4TZZ 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 provided for milestones in development and sales progress and graduated royalty income for sales after products enter the market.

The development code is the one requested by Cipla, 'CPN-101.' From Cipla's perspective, their desire to market it as an authentic new medicine is evident from the development code. The added phase I clinical trials started last September, and in January of this year, favorable results meeting the standards determined in cooperation with Cipla were achieved. Cipla is planning to transition to phase III as the next step after the added trials are completed. This is currently at the stage where Cipla is waiting for the applicable authorities, the FDA, to make their decision.



Development pipeline

Product name / Development code	Medicine development	Non-clinical	Ph- I	Ph-II	Ph-III	Application for approval	Launch
CPN-101(MRX-4TZZ) (central muscle relaxant patch using tizanidine)				April, 2017 A global development and sales licensing contract was executed with Cipla USA (with the exception of East Asia) January 2018: Added phase I clinical trial results released			
MRX-10XT (oxycodone transdermal patch for central analgesic)				February 2018: Phase I clinical trial results released			
MRX-5LBT (local anesthetic Lidocaine patch)				May, 2016 Announcement of results of phase I of clinical trials. Striving to get prompt approval for New Drug Application (NDA)			
MRX-5DML (donepezil and memantine transdermal patch for Alzheimer's disease)				Preparations for non-clinical trials.			

Development pipeline: present conditions and prospects (2)

② 'MRX-1OXT'

An adhesive skin patch containing oxycodone, one of strong analgesics (opioids). This is a pipeline, with which MEDRx is currently trying to use its technologies that use ionic liquid to create a transdermal tape-type medicine containing oxycodone, which does not easily penetrate skin. There are some calculations which estimate the total scope of the opioid analgesic market in the United States at 447 billion yen. Oxycodone is a massive market which comprises approximately 40% of this, and it is the pipeline the company most focused on. Non-clinical trials have been launched from November, 2015, and in December, MEDRx outsourced the task of manufacturing the investigational new drug to Tapemark, a manufacturer in Minnesota, U.S. (Since oxycodone is classified as a "narcotic for medical use", manufacturing it in Japan and then exporting it is not allowed.) Tapemark has an ample track record in development and manufacture of percutaneous absorption patches spanning over 60 years. Regarding the clinical trials started at the beginning of last year (phase I), in February of this year, the results were favorable and indicated both that "there is a high probability of achieving sufficient blood concentration of the drug" and that there were no side effects worthy of special mention observed. As the company moves forward with development, they will be simultaneously searching for the ideal partner to collaborate with.

③ 'MRX-5LBT'

An adhesive skin patch with lidocain, a local analgesic. The product is developed to be used for alleviating acute nerve pain associated with shingles. An investigational new drug application was submitted to U.S. FDA in February, 2016. Phase I was completed in May confirming the superiority of 'ILTS' technology. The fact that all went smoothly was made possible as there is a precedent, an adhesive skin patch 'Lidoderm', which scored a major hit in the U.S. (bringing in the peak period annual sales of 110 billion yen). Also, clinical trials of phase I implied some very good results. One is that the speed of percutaneous absorption of lidocain was faster than that of Lidoderm, and another is that with the area attached to the skin of only half (considerably smaller than that of Lidoderm), the amount of lidocain penetrating the skin per unit area of subcutaneous tissue is about 2.6 times more than that of Lidoderm. The clinical trials are currently underway and any new developments will be promptly reported to the company's investors.



Results of Operations

Performance (million yen, %)

Fiscal year end	Net sales	YoY	Ordinary income	YoY	Net income	YoY	EPS(¥)
December 2013	68	-21%	-616	-	-621	-	-
December 2014	26	-61%	-1,012	-	-1,016	-	-
December 2015	37	43%	-990	-	-878	-	-
December 2016	22	-40%	-1301	-	-1259	-	-
December 2017	198	787%	-988	-	-884	-	-
December 2018 (est.)	698	252%	-1115	-	-1100	-	-

- For the December 2017 period, net sales were 198 million yen (an increase of 787.2% over the previous period), with a passive balance in the ordinary profit and loss of 998 million yen (decreased passive balance), and a passive balance in net earnings of 884 million yen (decreased passive balance). Net sales increased because while the December 2016 period included only sales of Iodine Coating Ointment, December 2017 period included the contract lump sum payment of 1.5 million US dollars (170 million yen) for the licensing contract executed with Cipla USA for MRX-4TZT (CPN-101) (in addition to Iodine Coating Ointment) (recorded in net sales as earnings for research and development). In addition to the effects of the increase in sales, the sales and general administrative expenses made up mainly of research and development expenses were kept to 1,170 million yen (down from 1,350 million yen for the December 2016 period), subsidy income totaled 40 million yen, and gain on sales of shares of subsidiaries and associates totaled 90 million yen, resulting in significantly decreased passive balances.
- For the December 2018 period, anticipated net sales are 698 million yen (an increase of 252% over the previous period), with a passive balance in the ordinary profit and loss of 1,115 million yen (increased passive balance), and a passive balance in net earnings of 1,100 million yen (increased passive balance). Regarding the added phase I clinical trials of MRX-TZT, favorable results were announced at the end of January this year which met standards defined in advance in collaboration with Cipla. With milestone income from MRX-4TZT as a prerequisite, large-scale increase in sales is anticipated. MRX-1OXT and MRX-5LBT remain uncertain, so contract lump sum payments for them are not included in the predictions. In addition, the prerequisite research and development expenses are 1,562 million yen, a higher level than the previous period. These additional research and development expenses are due to smooth progress in the pipelines, so it is natural to interpret the increase in passive balances in a positive way.

If net sales of approximately 700 million yen can be achieved in this period as planned, it will be a high-level achievement unmatched since December 2011 period (740 million yen). This would be solid proof of 'De-ETOREAT' success.

Investment appraisal

- The company's lead pipeline, MRX-4TZT is proceeding smoothly. The company linked with Cipla, a pharmaceuticals company in India with a distinguished history, in April of last year (a big deal with milestone income potential of up to 30 million US dollars), and favorable results were achieved in the added phase I clinical trials conducted starting in September. The most important pipeline for the company, MRX-1OXT, has also released some good news recently. The phase I clinical trials started last year have achieved favorable results in human subjects. The sense of strong confidence gained from this announcement made an impression reflected in the management's comments, "We've made it over a really massive hurdle."

Currently, the company is simultaneously carrying out development and searching for a collaborator for MRX-1OXT. In April of last year, the announcement of their collaboration with Cipla on MRX-4TZT cause a spike in the stock prices, and if an MRX-1OXT licensing contract is announced, this will most likely have a major impact on stock purchases in the same way. We anticipate using their achievements in collaboration with Cipla to achieve a more advantageous position when choosing the next collaborator. For this company as well, choosing a collaborator quickly is not the goal. Instead, they want to carefully investigate their options to choose the best partner. The smooth progression of MRX-4TZT also gives them some freedom in funding for continuing development, which in turn gives them confidence.

- The three pipelines currently in phase I are proceeding smoothly with research and development, and there are no changes in their goals to acquire earnings through development collaboration and licensing out. The evaluation of bioventures depends on these two points. However, since the project is still only partially completed, major shifts in stock prices could have an impact. The only way to express the reason for this is in terms of market factors (it depends on how the Mothers market is affected by short-term individual investors). This conditions have worsened since the start of February due to global stock declines originating with the sudden drop in the US market. Although poor market conditions like this are precisely the time to buy individual stocks at low prices, however, we should be aware of adjustments to the support line formed by the 13-week moving average (around 1,300 yen) after October of last year.

Stock prices have risen dramatically since the start of this year due to a number of favorable announcements in succession. The rising prices themselves became a trigger for further increases, and many investors became aware of the company. However, since the prices reached a yearly high on February 5th (1,753 yen) with a larger volume of transactions than usual, we should be aware of selling pressure near this level. The total volume on this day was 4.2 million shares, and the average daily volume in 2017 was 452,000 shares, so the volume was equivalent to 9 business days. It seems the upper limit will remain at the same level until some new information comes out.

- In closing, the spread of opioid abuse is a social problem facing the United States. According to the government's calculations, the loss of productivity brought about by opioid addicts reached a top value of approximately 56 trillion (in 2015). If a stable supply of safe oxycodone patches enters the market, President Trump will probably be pleased as well. Implementing this product will save many lives in the United States and play a major role in the future of the country's children. We hope the market will take a long-term and magnanimous view of this Japanese company attempting to develop this kind of medicine.



(Okamura)

Stock Price (historical)

Year high	¥1,753
Year low	¥453
Highest since the IPO	¥7,500
Lowest since the IPO	¥341

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