MEDRx（4586） TSE Mothers

Although the clinical trials of ETOREAT ended with failure, several promising pipelines for the U.S. are moving ahead.

Yuya Okamura, Analyst

Company profile	
Location	Higashikagawa-shi, Kagawa
Representative	Masayoshi 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 August 31)	
Stock price	¥551
Outstanding shares	8,514,700 shares
Trade unit	100shares
Market cap	¥4.69billion
PER (est.)	-
EPS (est.)	-
PBR (actual)	1.68x

■ 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. With 'MRX-5LBT', an adhesive skin patch with lidocain, a local analgesic, the company has completed phase I in May confirming the superiority of its 'ILTS' technology. The 'MRX-10XT', an adhesive skin patch containing oxycodone is scheduled to enter phase I already in 2017. Non-clinical trials have already started for 'MRX-4TZT', an adhesive skin patch containing tizanidine, a centrally acting muscle relaxant, and the product is due to go into phase I in the U.S. by the end of this year. The company is thus simultaneously getting along with a number of promising pipelines.

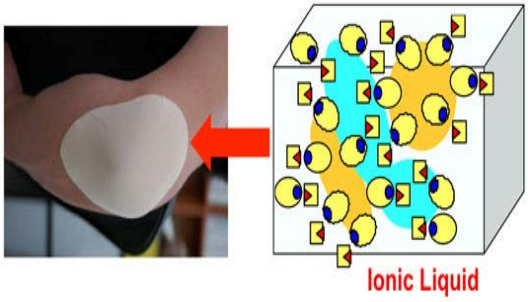
■ Development costs shrank due to a change of plan with ETOREAT.

For the current term ending December, 2016, the company expects volume of sales of 29 million yen (a 20.3% decrease compared with the preceding term), a passive balance in the ordinary profit and loss of 1,594 million yen, and a passive balance of net earnings of 1,572 million yen. As the expenses incurred in connection with the DOMS test of ETOREAT were less than expected, the current account deficit is less than what was stated in the plan made in the beginning of the term. The four pipelines excluding ETOREAT that MEDRx' is simultaneously promoting are making satisfactory progress, and although the current account deficit will expand compared with the first half of the year, it will expand for the forward-looking reason of an increase in the expenses needed for clinical and non-clinical trials.

■ Distributing management resources intended for ETOREAT to quickly play more and more strong cards.

Although development of ETOREAT was frozen, the company still has a number of cards to play as it is preparing several pipelines. With both MRX-1OXT and MRX-4TZT, it is possible to "directly discern the efficacy of the medicine from blood concentration," and phase I shall lead directly to Proof of Concept. That is why it seems likely that the company will be able to go quite swiftly from the conclusion of phase I to profits. As the company has been raising money to ensure good financial footing, the cash equivalent, which was 2,060 million yen as of the end of December of last year, increased to 2,790 million yen as of the end of June of this year. For the time being, the problem of financing is thus cleared and the company is pushing on towards new targets using the strategy of portioning out management resources to pipelines other than ETOREAT.

Point summary (1)



●What kind of company is MEDRx?

MEDRx is a venture company established in January, 2002 in Higashi-Kagawa-shi, Kagawa. Masayoshi Matsumura, the founder and the current President 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 first topical tape product for the U.S., country boasting an enormous pain-relief market. In February, 2013, MEDRx was the first bioventure from Shikoku to achieve an IPO at the Mothers of the Tokyo Stock Exchange.

●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 also acquired medical patent for every pipeline.

●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.

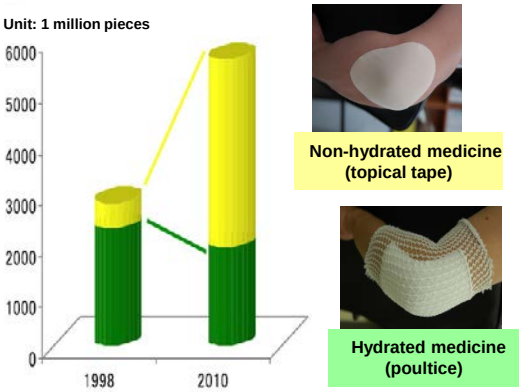
(1) The first is that the pharmacologically effective agent is released gradually. Because the medicine comes out slowly, it is easier to keep blood concentration constant and continuously maintain benefits of the drug.

(2) The second is that as the medicine does not have to pass through the liver unlike orally taken medicine, it does not remain there. Side effects are thus less likely to emerge.

(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 successful examples of adhesive skin patches?

One example is Mohrus Tape made by Hisamitsu Pharmaceutical (efficacy: osteoarthritis, etc.). Today, the annual sales of the entire range of the Mohrus Tape products are running at just over ￥60.0 billion making this a major, revenue-generative product. Formerly, the only kind of anti-inflammatory analgesic patches available was the hydrated type - plasters containing water. As the cooling effect of such plasters was caused by evaporation of moisture content, they gave the user a pleasant, cooling feeling when applied to the skin. Hisamitsu Pharmaceutical, on the other hand, succeeded in developing their Mohrus Tape – a topical tape that did not contain any water. Their products do not come off easily so they can also be used in sports just as they are. Also, they do not dry out like the hydrated type plasters, which need to be changed several times a day as the water evaporates, and thus save the user time and effort. Hydrated type patches have already lost in market share to the non-hydrated ones in the Japanese market (if we take a look at Hisamitsu alone, the annual sales of the entire range of the Mohrus PAP products are about 6 billion yen adding up to a mere 1/10 of the tape product group).

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

Simply put, the U.S. people are a ʻpopulation that is prone to painʼ. Although the mainstay of the market of medicine for sharp pain in the U.S. is medicine for internal use, the Americans, who are weaker than Japanese people when it comes to pain, are using very strong analgesic drugs – morphine and other opioids. And MRX-1OXT is the pipeline, with which the company is trying to create a transdermal therapeutic drug blending its ILTS technology with oxycodone, a drug that holds the top share in this opioids market.

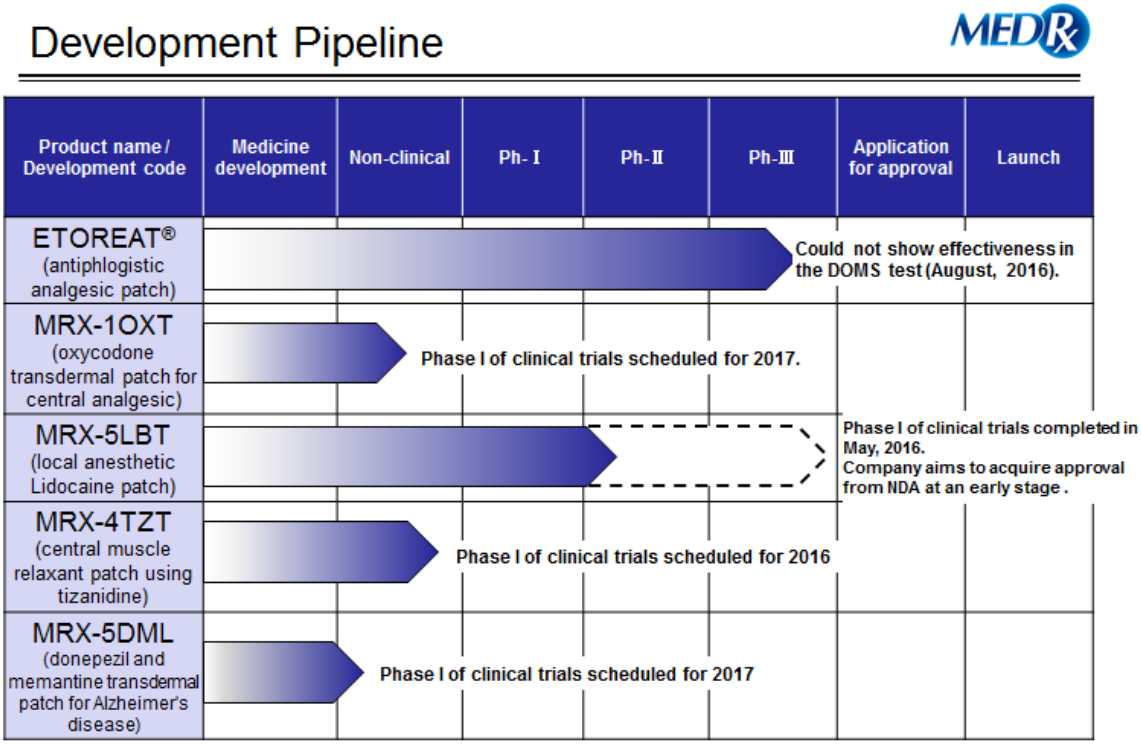
In the U.S., the adhesive skin patch market has been already expanding since 2008 with products for mild to moderate pain. The pioneer of this trend was ʻFlectorʼ by Teikoku Seiyaku, for which the President of MEDRx, Matsumura had served as vice president. ʻFlectorʼ was quite successful after its release in 2007 and ʻLidodermʼ, which was released after that, was enormously successful. The two together scored sales in the 100 billion yen per year class (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 expanding with new medicine being developed for depression, ADHD, Parkinson, Alzheimer, and other diseases. The unit prices per single patch for these adhesive skin patches are worthy of special mention in this regard. In Japan, one Mohrus Tape sells for around ￥40 a piece, but the same item is sold for approximately ￥800 a piece in the U.S. Now, this can be held up as simply a textbook example of the operation of the price setting system in the U.S. but the scale of the fat profits to be gained if MEDRx manages to become the first topical tape supplier in the U.S. is quite substantial.

Development pipeline: present conditions and prospects (1)

① 'ETOREAT' → Fails in phase III; future plan will be determined upon discussion with the partner.
'ETOREAT'(an anti-inflammatory analgesic patch) was the company's most important pipeline with which it tried to become the first topical tape supplier in the U.S. Although in phases II/III, placebo (drugs not containing any active/effective elements) comparison tests have established a statistically significant differential in efficacy in comparison to the placebos, the drug ran into difficulties in the second stage of the clinical trials commenced in December 2013. FDA (Food and Drug Administration), the U.S. regulatory agency, required an additional clinical trial because depending on methods of analysis, a statistically significant differential was, in fact, established.

For this additional clinical trial, the FDA gave the company a new test model comprised of tests for DOMS (delayed onset muscle soreness), and the trials were commenced in March, 2016 (observation of the last case was completed on July 22). The trials involved artificially inducing DOMS in 101 healthy test subjects and then checking the effectiveness by monitoring any reduction in pain. The company had high hopes for the outcome, but the result that was announced on August 22 said **"no statistically significant differential in comparison to the placebos found."** Regrettably, this time clinical trials ended with failure.

First and foremost, MEDRx intends to analyze the data of the clinical trials, and then **decide what course to pursue in the future upon discussion with KOWA, its partner.** Although the plan was to submit an application for approval next year and receive a milestone income (1,050 million yen) from KOWA, all these plans are now shelved.



Development pipeline: present conditions and prospects (2)

②"MRX-1OXT"

'MRX-10XT' is 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 topical tape-type medicine containing oxycodone, which does not easily penetrate skin. With the pain-relief market in the U.S. alone worth some ￥1 trillion and opioids holding a share of about half of the total, it is reasonable to believe that oxycodone holds about 40% of the opioid share (oxycodone accounts for around 200 billion yen of the market).

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. **Launch of clinical trials (phase I) is scheduled for 2017.**

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 120 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.**

④"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. Non-clinical trials are already under way and **the product is scheduled to enter into phase I by the end of this year in the U.S.** The market of neuromuscular junction blocking drugs in the U.S. is very large with trial calculations putting it at approximately 120 billion yen. By marketing these drugs in the form of adhesive skin patches, it is possible to improve the durability of effective blood concentration and also reduce such side effects as liver damage and sleepiness.

⑤"MRX-5DML"

An adhesive skin patch with two therapeutic agents for Alzheimer. A medicine with the two ingredients for internal use is already on the market. If it can be made in the form of an adhesive skin patch, it is possible to deal with risks of patients forgetting to take the medicine or forgetting they took it and taking it again exceeding the dosage. The adhesive skin patch is scheduled to go into phase I in 2017.

Results of Operations

Performance（million yen, %）

Fiscal year end	Net sales	YoY	Ordinary income	YoY	Net income	YoY	EPS(¥)
December 2011	741	154%	-479	-	-433	-	-
December 2012	87	-88%	-578	-	-571	-	-
December 2013	68	-21%	-616	-	-621	-	-
December 2014	26	-61%	-1,012	-	-1,016	-	-
December 2015	37	43%	-990	-	-878	-	-
December 2016 (est.)	29	-20%	-1,594	-	-1,572	-	-

● For this term (term ending December, 2016), MEDRx expects net sales of 29 million yen (a 20.3% decrease compared with the previous term), ordinary loss of 1,594 million yen (an increase of deficit), and net loss of 1,572 million yen (an increase of deficit). Although the company assumed ordinary loss of 2,100 million yen, the results of the DOMS test for "ETOREAT", which were expected to come in the first half of the term, only came in the second half of August. As a result, expenses incurred in connection with the DOMS test were less than expected, which is why the forecast of performance results was corrected on August 5.

However, the announcement of the results of DOMS test for "ETOREAT" meant that the drug failed at the stage of phase III. As the development costs for the second half that were intended for ETOREAT are no longer needed, there is a possibility that the current account deficit will be lower than the value revised as of August 5. The four pipelines excluding ETOREAT that MEDRx is simultaneously promoting are making satisfactory progress. The current account deficit will expand compared with the first half of the year but for the forward-looking reason of the increase in the expenses needed for clinical and non-clinical trials (research and development costs).

Investment appraisal

● While the company made very good progress with "ETOREAT" and the application for approval was before its very eyes, the DOMS test ruled that there was no statistically significant differential in comparison to the placebos. The wall that the company ran into was the fact that pain is an area where effects of the medicine cannot be expressed numerically. Moreover, it may be that the national character of the Americans who were subjects of the test also affected the results. One American pharmaceutical trade journal has published a paper written by a university research group, and, basing their conclusions on a survey of clinical trials results for medicine for sharp pain released in the past 23 years, the research group asserts that the difference between placebos and real medicine in recent years has been substantially shrinking. They also state that this tendency has not been observed in Asia or Europe. And the reason they give for it is that as the U.S. allows advertisement for consumers by pharmaceutical companies, the subjects, who have seen such commercial messages advertising the effect of medicine, might have held excessive expectations for medicine, which may have induced the placebo effect.

● It is surely regrettable that development of ETOREAT will be frozen. However, the company has been promoting four more pipelines at the same time. The company still has a number of cards to play, and with MRX-1OXT, MRX-4TZT, and MRX-5DML it is possible to “directly discern the efficacy of the medicine from blood concentration.” Thus we can surmise with a fair degree of certainty that the effectiveness will be confirmed at the stage of phase I. Therefore, MEDRx will most probably be able to go more swiftly from the conclusion of phase I to profits. Also, as luckily the company has been raising money to ensure good financial footing, the cash equivalent, which was 2,060 million yen as of the end of December of last year, increased to 2,790 million yen as of the end of June of this year. For the time being, the problem of financing is thus cleared, and all the company needs to do is to portion out management resources to pipelines other than ETOREAT. Using a successful pipeline such as MRX-1OXT, which smoothly cleared phase I, if the company manages to find a business partner to shoulder the marketing side at an early stage, it can quickly launch the product in the market without making large investments.

● The price for the company stock made a sharp rise from March when the DOMS test was started and continued high until April, when the whole Mothers market was on the rise. However, it dropped sharply in response to failure in the DOMS test, and the large scope of transactions shows that there was a large number of investors, who were expecting a success, and sold on disappointment. Although the stock price went back to square one, I have confirmed with the present management that their eagerness to make adhesive skin patches for the U.S. market has not changed at all. MEDRx also has high technical capabilities. To achieve the big goal in front of it, the company is now turning a new leaf in its history, and what we are seeing now is just a several-year delay. I strongly believe that although there are speculators, who have abandoned ship without thinking much about it, there is no need to be overly pessimistic.

（Okamura）

Stock Price (historical)	
Year high	¥1,629
Year low	¥341
Highest since the IPO	¥7,500
Lowest since the IPO	¥341

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