INTRODUCTION
SKIN IN THE GAME: TRANSDERMAL DELIVERY AS A NEW SOURCE FOR BIOPHARMA INNOVATION

By Kevin Pang, PhD, MBA

Transdermal delivery technologies, despite great promise, have thus far failed to live up to their potential as powerful delivery devices for the sustained and controllable delivery of active pharmaceutical ingredients (APIs). Although an almost-30-year-old platform technology, today only about 16 drugs are actively on market for delivery via transdermal patches. Hurdles to adoption range from cultural and consumer preferences, to drug abuse problems, to limited API application due to solubility and penetration issues.

However, we believe that this is about to change in a big way. The convergence of advanced formulation technologies, combined with printed electronics, will transform the adhesive transdermal patch platform into a new fifth generation of devices and a new source of delivery innovation for biopharma companies and patients (Figure 1).

Current or fourth-generation platform technologies use active or electronic delivery, e.g. Nupathe's (now Teva) iontophoretic sumatriptan patch. The combination of active delivery with advanced formulation for enhanced skin penetration constitutes our definition of a fifth-generation platform.

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The unique strength of transdermal patch delivery is the ability to deliver constant regulated levels of API for the treatment of chronic conditions. Treatment of neurological diseases and conditions like Parkinson's disease, depression and pain are extremely well suited to this unique strength, avoiding the typical peak and trough phenomena experienced with oral solids (Figure 2) as well as first-pass clearance for greater sustained bioavailability. An example of this is Nupathe's 2013 US FDA-approved iontophoretic sumatriptan delivery patch for migraine, prompting Teva Pharmaceuticals to quickly purchase the company for its battery powered transdermal patch franchise and technology platform.

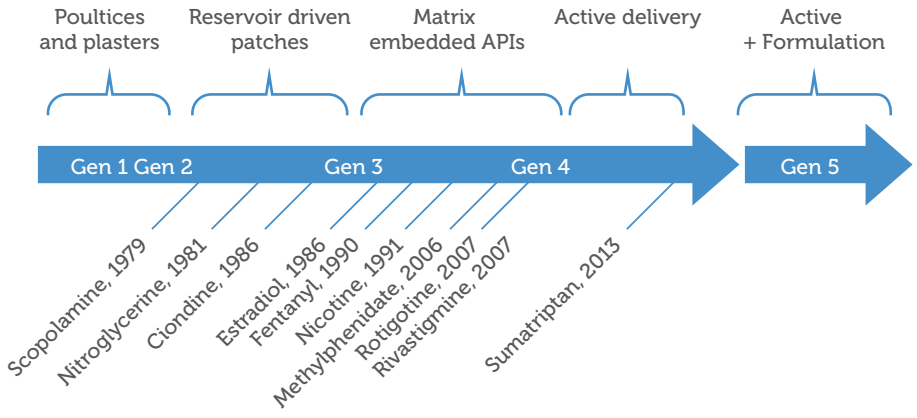

Figure 1: A brief and compressed history of transdermal delivery.

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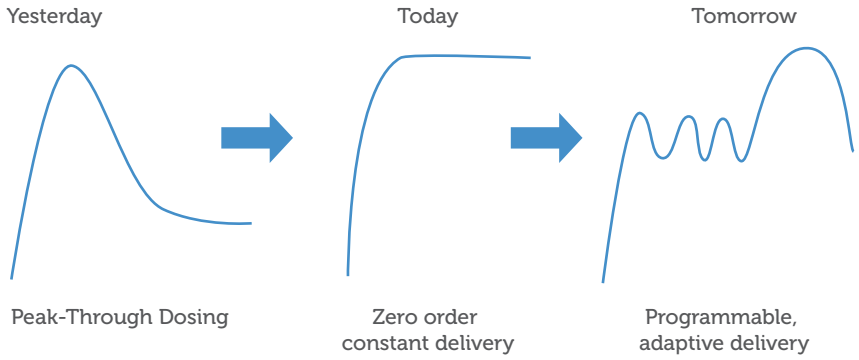

Figure 2: Transitioning into increasingly sophisticated delivery paradigms.

Electronics enables much more constant and dose effective delivery today. Increasing sophistication and application of software, algorithms, sensor incorporation, web and analytics, along with increasingly effective at-will skin penetration and delivery, will drive personalised and adaptive drug delivery.

The promise of thin, flexible, printed circuits and batteries layered on top of the transdermal platform is the increasing potential capability to titrate and customise drug delivery, in effect, personalising drug delivery tied to an individual's metabolism and disease state. Further convergence and application of advanced microfluidics, sensors, and web-based analytics will enable the eventual build of powerful biofeedback loops for even more exquisite near real-time modulation. At the same time, innovators in the sector will push the miniaturisation frontier, resulting in increasing ergonomics and comfort, and lower the development and production cost curves.

As a result, we believe transdermal drug delivery is in the midst of experiencing a renaissance in development and application as part of the armamentarium of intelligently and co-ordinately dealing with multiple medication management. Advances in micro- and nano-needle technology (e.g. Micropoint); the use of ultrasound (e.g., Transdermal Specialties), iontophoresis (e.g. Nupathe), electroporation (e.g., Ichor Medical Systems), and even heat generation (e.g., MedPharm), more effectively to drive drug delivery; the use of printed electronics and algorithms to create feedback loop driven mini-pumps; and advances in physiological knowledge with integration into circadian rhythms, will enable transdermal patches to be much more powerful and functional to the patient.

The number of transdermal patch-delivered drugs in clinical trials provides a rich landscape by which technology providers can partner with drug companies to enhance functionally and create multiple product line extensions in the future. An estimated 81 clinical trials are ongoing currently, more than half for nervous disorders, pain management, and behaviour modification such as drug and smoking cessation (see Figure 3).

One of the major barriers to skin-based delivery is the low permeability of skin that makes it difficult to deliver molecules greater than 500 Da in size. Figure 4 details a few examples of companies that are working on advanced formulation to enhance delivery, not just of small molecules, but even biologics of 106 Da or greater in size, as either biological drugs or vaccines. Many are working on enhanced large molecule delivery, including biomolecules such as hyaluronic acid, vaccines, enzymes, and potentially therapeutic antibodies.

We predict that combining active electronic delivery with advanced formulation will provide unprecedented innovation by expanding the size range of deliverable APIs, and efficacy of delivery of APIs, greater bioavailability, and controlled release that is not just chemical and thermodynamically derived, but electronically enhanced and programmed per individual. Fifth-generation transdermal delivery should not only open up more effective and efficacious ways to deliver drugs to patients, but also provide new forms of intellectual property extension for biopharma companies.

To provide an example of how big and dynamic we expect the transdermal patch drug delivery market to grow, we

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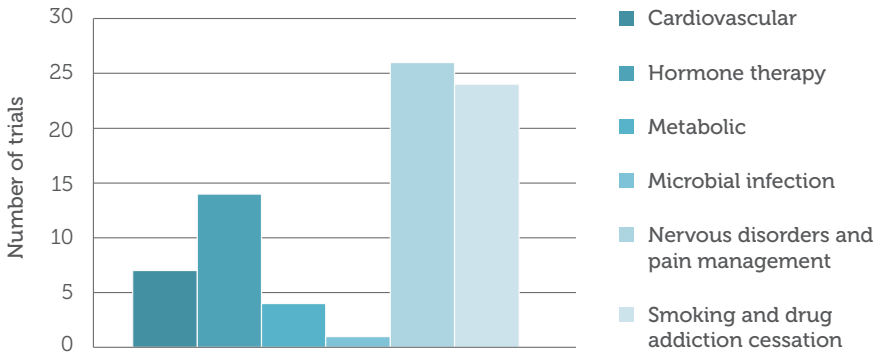

Figure 3: A robust clinical trial pipeline.

Company	Technology
Halozyme	Hyaluronidase skin penetration enhancer for biologics
Apricus Biosciences	Small molecule amphiphilic amino acid-fatty acid moiety skin penetration enhancer
Nanocyte	Sea anemone injectors to form channels in skin
JRX Biotechnology	Oils/alcohol/PEG formulation for large molecule delivery
Salvona Technologies	Micro- and nano-encapsulation platform
Transdermal Technologies	Polar solvent matchup to API for ionic liquid formation
Convoy Therapeutics	11-mer peptide skin penetrant directly conjugated to API or embedded in liposome
NewGen BioPharma	Multiphase oil:water emulsion (licensed from Novavax)
Nuvo Research	Membrane penetration enhancers + heat generation

Figure 4: Example companies developing skin penetration enhancement technologies.

constructed potential demand curves for Nupathe's (now Teva) sumatriptan iontophoretic delivery patch for chronic migraine (see Figure 5). Conservative estimates of prevalence growth and market penetration still indicate the potential for a blockbuster drug for Teva by 2021, despite the API, sumatriptan (Imitrex™) being generic, and available for injection via prefilled syringe. Patch convenience, which obviates the need for patient self-injection; and the ability to program desired kinetics, we believe are powerful drivers in favour of this revitalising delivery platform.

Given the 81 ongoing clinical trials, it seems likely that some will be approved. If we assume that only 20% are US FDA- and/or EU EMA-approved over the next 2-3 years, then we can expect to see at least 16 new transdermal patch products come to market. While each market is different, in general our model assumes 9-10 years from launch to peak year sales, that many of the targeted disease indications will yield opportunities in the US$500 million to $1 billion peak year sales levels, we therefore expect to see up to an additional $10 billion in annual sales via transdermal patch delivery by 2025.

Even a few successes with the current pipeline would be highly stimulatory for further innovation in this field. The predicted three ball collision between pharma, electronics, and formulation and delivery companies will give rise to fifth-generation devices. We see several non-traditional players poised to participate in the transdermal patch drug delivery evolution. Examples include: Blue Spark Technologies, which is already targeting thin-film printed batteries for patches; PragmatIC Printing, which prints logic circuits for potential sensor hookups; and ThinFilm's recent acquisition, Kovio Technologies, which combines its printed memory and sensor platform with near field communications for wider range communication (e.g. remote analytics and services). Conversely, firms like MC10, which prints flexible adhesive integrated circuits for remote biosensing, might themselves evolve to become drug delivery platform companies.

The potential for personalised delivery of vaccines, nutrients, and both small- and large-molecule drugs via intelligent transdermal patches is here. Furthermore, the true potential of personalised delivery lies in the integration of physiologic feedback loops, i.e. sensors and analytics to create low cost, accurate, highly convenient patches, perhaps linked to services, making the transdermal patch a truly powerful platform.

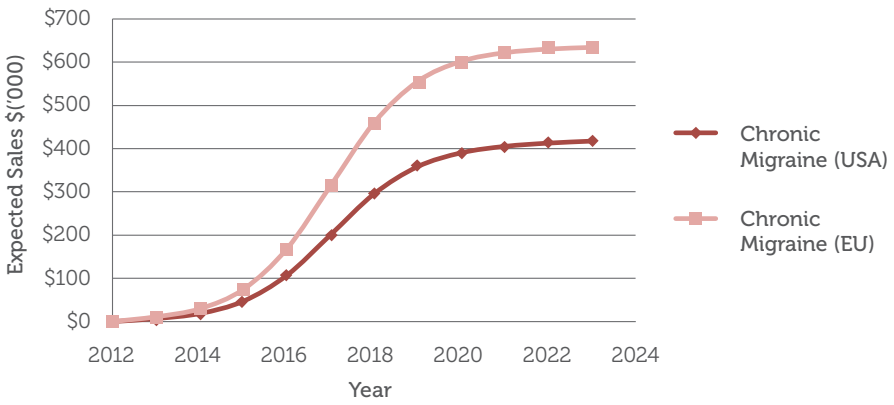

Figure 5: Estimated demand curve for Zecuity based on chronic migraine prevalence and incidence rates in the US and EU. (Application is assumed for chronic migraine only and forecasted out 10 years from 2013. Total sales expected to hit $1B by 2021. Nupathe estimates that key patents covering their platform extend through 2027, covering our forecasted range.)

Kevin Pang, PhD, MBA, was the lead analyst on the Lux Research report, "Skin in the Game: The Coming Rise of Transdermals", which was published in January 2014, and is available to clients of Lux Research. Find out more at: https://portal.luxresearchinc.com/research/report_excerpt/15923.