PHARMA LATCH ANGLED **MICRONEEDLE** PATCH FOR ENHANCED DRUG AND VACCINE DELIVERY

Nicky Bertollo, PhD, Co-Founder and Chief Technology Lead, Ronan Byrne, Co-Founder, and Andrew Muddle, PhD, Advisory Board Member, all of Latch Medical, introduce Pharma Latch – a user-centric angled microneedle patch technology. They discuss its key benefits, such as dramatically increased payload potential, precision, low cost and variable patch-wear times, and highlight how Pharma Latch has the potential to overcome many of the limitations of existing routes of administration for therapeutics and vaccines.

Intradermal delivery holds great promise as an attractive alternative to traditional oral and parenteral routes of administration for the delivery of vaccines and therapeutics, including biologics. Systemic uptake of therapeutics via the dermal blood capillaries has a host of benefits, including avoiding the deleterious effects of first-pass metabolism, rapid drug onset and improved bioavailability of APIs, such as biologics, that are not readily absorbed across the mucosal layers of the gastrointestinal tract. Furthermore, the skin is replete with antigen presenting cells (APCs) and therefore represents an optimal location for the delivery of vaccines (both traditional and novel DNA- and mRNA-based vaccines) in order to elicit an enhanced immune response.

Methods employed to deliver or diffuse drugs into the dermis must compete against the skin's excellent barrier function – and are associated with known limitations as a result. Invasive intradermal injections using hypodermic needles, pen injectors and even needle-free injectors are associated with the potential for discomfort and distress for the patient; have significant requirements around infrastructure, training of personnel and sterile settings; and have the ever-present risk of needlestick injuries. Transdermal patches overcome some of these limitations but are confined to a relatively small number of compounds which are known to be able to successfully permeate the intact outer layer of skin – the stratum corneum – either passively or in combination with permeation enhancers.

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These and other restrictions have motivated the development of minimally invasive microneedle patch (MNP) technologies which not only overcome many of these limitations but – as noted by the World Economic Forum in its list of Top 10 Emerging Technologies of 2020[1] – have the potential to play a role in transforming healthcare. The enhanced intradermal delivery attributes offered by MNPs have the potential to cater for existing, repurposed or new ranges of compounds not suited to the established routes of administration.

Pharma Latch is a revolutionary MNP technology that unlocks a delivery solution that addresses a wide variety of drug and vaccine delivery challenges faced by both conventional routes of administration and current MNP technologies.

INTRODUCING PHARMA LATCH

Pharma Latch is an easily self-administered, self-anchoring, solid-coated MNP optimised

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Figure 1: Pharma Latch microneedle patch technology. (Image courtesy Latch Medical. Reproduced with kind permission.)

for therapeutic and vaccine delivery (Figure 1). Pharma Latch technology exhibits opposing arrays of angled stainless-steel microneedles (MNs) coated using a proprietary process performed at room temperature which dries instantaneously and is compatible with a range of compounds, including biologics.

Pharma Latch is applied to the skin using a simple and intuitive clicking action. This manual clicking moves the opposing angled MNs towards one another, penetrating the outer skin layers and drawing the skin onto the MNs in a controlled, repeatable fashion. Robust, adhesive-free and instantly reversible attachment to skin can be achieved. This, coupled with inherent tailorability in both design and coating, means that Pharma Latch can facilitate both short- and longer-term patch wear and drug elution times (seconds/minutes/days/weeks) across a range of compound types at much higher payloads than are currently achieved by existing solid-coated and dissolvable MNP technologies.

Key features and benefits of Pharma Latch's technology include:

- **Increased MN surface area available for coating.** When compared with the conventional vertical approach taken by MNPs, the angling of the Pharma Latch MNs – specified for a given depth target in the skin – results in greater surface area available for coating with the API.
- **Superior coating concentration across a range of compound types.** The proprietary coating technology produces coatings at room temperature and without the need for linkers or binders, meaning that APIs may be formulated and deposited at relatively higher concentrations. The process deposits API-containing formulations in uniformly even and thin layers, which preserves MN tip geometry to a greater extent than traditional dip-coating techniques..
- **Increased payload potential.** The combination of these geometry and coating factors can elevate the payload potential of the Pharma Latch far beyond what is currently achieved by solid-coated and dissolvable MNP technologies.
- **Stable coatings.** The proprietary coatings can potentially be stable at room temperature, which removes cold-chain and logistics requirements, facilitating global, remote distribution. Pharma Latch has demonstrated with a number of biological APIs that the coating process does not affect its stability.
- **Robust, adhesive-free attachment.** The unique manner in which the angled MNs interdigitate with and anchor to the skin removes the need for chemical-based adhesives. This also opens up the possibility of long-term patch wear from hours and days up to several weeks – a possibility not achievable using existing solid-coated MNP technologies.
- **Highly user-centric design and ease of use.** The Pharma Latch is applied to the skin using a simple and intuitive manual clicking action and is easily removed. Built-in safety mechanisms prevent accidental deployments, whilst visual, tactile and audible feedback is provided to the user on successful attachment. The user-centric and intuitive design has no training requirements, allowing for administration by minimally trained medical personnel or self-administration by patients.
- **Repeatable, reliable penetration and depth targeting.** Uncontrolled and variable skin deformation occurs during the application of conventional MNPs to skin, resulting in partial, incomplete and highly variable embedding of the full MN height.[2,3] In some cases, only a small proportion (up to 30%) of MN height is routinely exposed to skin.[4] Variable, incomplete MN penetration may potentially reduce payload delivery efficiency for both conventional solid-coated MNPs and dissolvable MNP technologies.[3,5] The unique method of engagement applies subtle traction to skin during deployment, drastically reducing deformation and ensuring near full-length (>95%) exposure of the angled

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MNs to skin.[6] The superior penetration efficiency of Pharma Latch's angled MNs could result in reduced dosing variability, which will be observed in drug absorption measured in the pharmacokinetic data of its products.

- **No reliance on pre-energised applicators.** Many MNP solutions looking to deliver higher payloads need a high-density MN configuration. These need a high-velocity impact onto the skin to aid penetration – requiring a pre-energised applicator. This also limits potential patch size. Pharma Latch's controlled mechanism of engagement with skin removes the reliance on pre-energised applicators and increases the range of permissible patch sizes from 4 cm^2 upwards.
- **Configurable to meet treatment objectives.** The Pharma Latch platform can be readily adapted to meet varied treatment objectives, including human factors considerations, with one- or two-part configuration options to facilitate both short- and long-term wear and delivering low-to-high payloads.

ENGINEERING THE PHARMA LATCH

The Pharma Latch is optimised for skin penetration and adhesive-free attachment. The unique solution ensures that each individual angled MN is repeatably inserted to the same depth in the skin every time in every patient.

Mechanism

Subtle traction is applied to the skin by the opposing arrays of angled MNs keeping the skin taut and dramatically reducing skin deformation during insertion. This novel mechanism of insertion is illustrated in Figure 2. Conceptually, the net effect of these attributes results in skin being drawn up onto the Pharm Latch MNs in a controlled, repeatable fashion.

The mechanism of insertion differs fundamentally from many existing MNP technologies and application techniques (including both manual pressing and high-speed impact using pre-energised applicators) which effectively act to push the skin away from the patch as it is being applied. As mentioned prior, the variability in MN penetration across existing MNPs is well reported in the scientific literature. Importantly, the extent of this deformation can be exacerbated by the anatomical location and integrity of the skin, as well as by subdermal fat.[7] The combination of these patient-related and skin biomechanics factors can be expected to give rise to dosing variability across repeated applications on the same patient (i.e. intra-subject variability) and/or between patients across a population (i.e. inter-subject variability) when treated using conventional MNP technologies.

Repeatability

The Pharma Latch deployment mechanism is designed to produce repeatable MN insertion, independent of skin type or anatomical location. This substantially reduces intra-subject and inter-subject dosing variability risks, which may be observed in pharmacokinetic data. The increased penetration efficiency achieved by the Pharma Latch MNs, derived from a combination of the angled MN geometry and skin insertion mechanics, ensures repeatable,

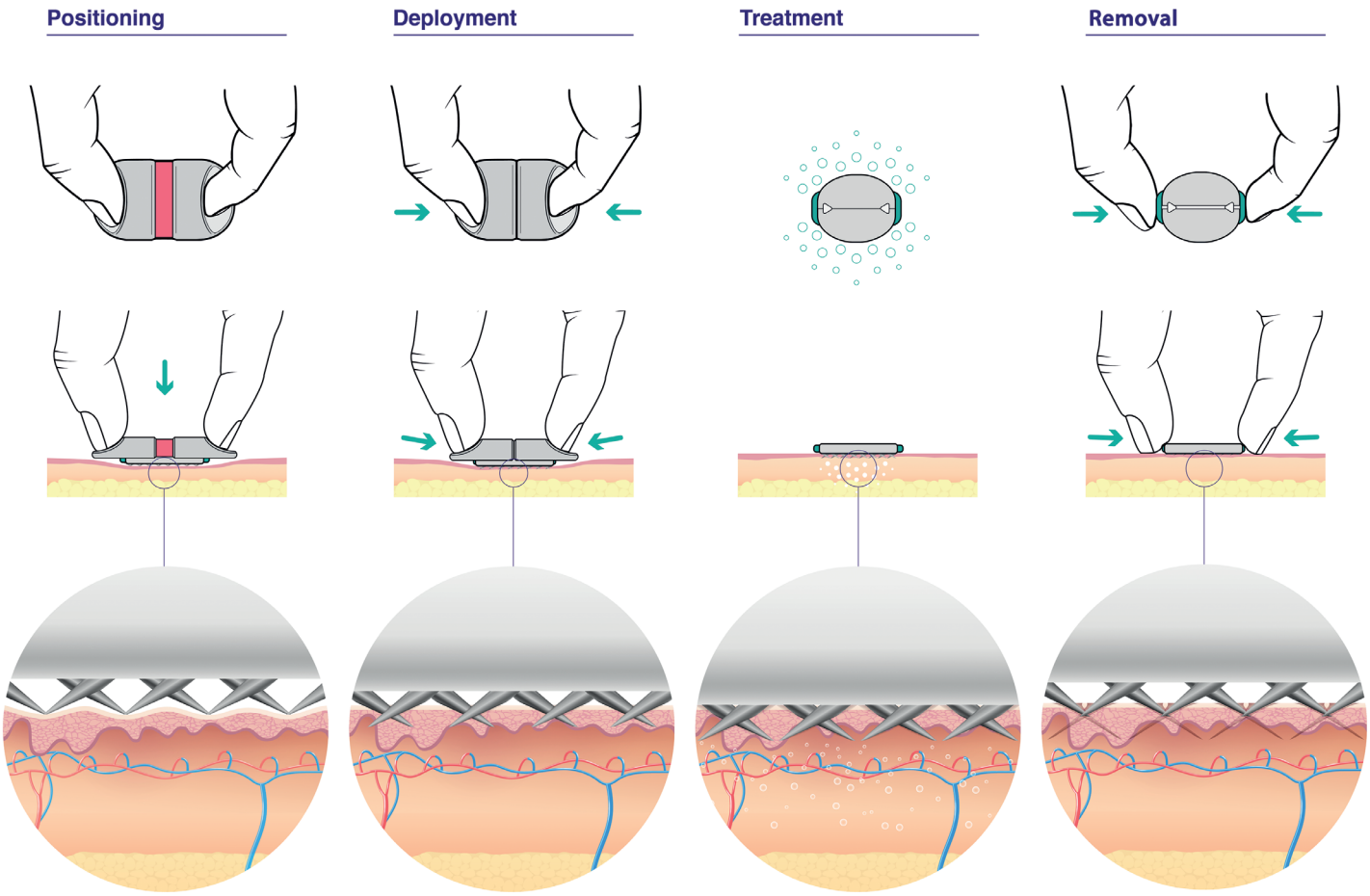

Figure 2: Schematic depicting Pharma Latch's mechanism of engagement, the subsequent release of the API from the fully embedded angled microneedles and the method of removal.

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near-full-length coated MN exposure and release of API into the interstitial fluid of the skin for systemic uptake.

Manufacturing

The increased MN insertion efficiency of Pharma Latch, coupled with a controlled, manual application action, removes the need to employ costly, high-strength metal alloys. Pharma Latch uses low-cost, surgical-grade stainless steel and can be produced using scalable, low-cost production methods leveraging standard pharmaceutical packaging materials and processes. Coating of the MNs relies on a highly automated process with established high-volume, low-cost techniques.

Tailorability

Pharma Latch is highly configurable and both the core MN platform and coating process can be readily tailored to meet the treatment objectives, in terms of desired payload, release kinetics and wear times. Pharma Latch offers an unsurpassed ability to target specific depths in the skin, owing to its superior penetration efficiency (>95% length penetration),[6] which may be important when treating certain dermatological conditions or administering vaccines. The direct implication of a highly efficient MN insertion is that vertical penetration depth is ultimately governed by the MN geometric parameters and, specifically, the vertical MN tip height from the substrate, which can typically be engineered to be in the range of 250–600 µm or beyond.

The scalable approach to MN fabrication ensures that the Pharma Latch design (i.e. MN geometry, tip height, number and density) is readily customisable to accommodate the desired payload and intended release kinetics of the deposited coating. MN density can be tuned to meet the payload objectives of the specific application, which gives rise to a range of potential Pharma Latch configurations. Pharma Latch makes use of a two-part system (with reloading capabilities) for high-density MN patch configurations supporting high payloads, with the second part increasing the mechanical advantage and promoting usability. A one-part system is available for lower payload, low-MN-density applications.

Coating

Pharma Latch's solid MNs coated with API offer an advantage over dissolvable MNP technologies in that the solid MNs themselves provide the mechanical backbone and requisite strength. This potentially simplifies the mechanical considerations around – and specific requirements of – excipients in a given formulation. This approach, coupled with the method of coating, can simplify the formulation process, whilst simultaneously increasing the range of compound types that can be readily incorporated into the platform.

Payload

The tailorability in the proprietary coating process allows the delivery of payloads far in excess of what is currently being achieved by solid-coated and dissolvable MNP technologies. Combined with the self-anchoring angled MN geometry, this potentially allows Pharma Latch to rival the dosages currently being delivered through more traditional means. As a result, Pharma Latch has the potential to offer a step change in MN-mediated therapeutic and vaccine delivery.

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FUTURE OUTLOOK

The Pharma Latch technology is technically validated and currently moving towards a number of pre-clinical studies with a range of different compounds and vaccines. The simplicity of Pharma Latch, combined with its payload potential, opens up a variety of new possibilities – both in the MN drug delivery sphere and also in a broader consideration of drug delivery opportunities previously considered out of reach for MNP technologies.

The company is actively seeking collaborations with companies looking to develop novel products which meet currently unmet patient needs – be they existing compounds or vaccines, generic APIs looking to differentiate through the 505(b)(2) route of registration in the US or new compounds or vaccines looking to be delivered intradermally, be they small molecules, vaccines or biologics.

ABOUT THE COMPANY

Latch Medical is a venture-funded company with a platform microneedle technology. The technology is centred on opposing arrays of angled microneedles that can penetrate the outer layers of the skin in a manner ensuring consistent needle penetration and without the use of any adhesive. The platform can be used in a number of different applications, including drug delivery, biosensing and wearables. In 2019, Pharma Latch was awarded a substantial grant by the Irish government. A rapid development plan ensued, allowing the Pharma Latch technology to progress.

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ABOUT THE AUTHORS

Dr Nicky Bertollo, PhD, is the inventor of the Pharma Latch angled microneedle platform technology and a medical device innovator. He has over 15 years' experience in the design, development, preclinical testing and evaluation of medical devices and technologies, publishing more than 40 research articles from this work. He has more than 25 issued or pending patents which have been licensed to multiple start-up companies, including Latch Medical, which he co-founded.

Ronan Byrne is a highly experienced Chief Executive Officer and commercial leader of multiple companies over the last two decades. His speciality is commercialising innovative medical technologies. He founded, built and led the development of an ophthalmic diagnostics company – ClearSight Innovations – which was sold to a global industry leader in 2015. Mr Byrne acts as an evaluator and panellist for organisations such as Enterprise Ireland and is an advisor and mentor to multiple life sciences companies.

Dr Andrew Muddle, PhD, Advisory Board Member at Latch Medical, is a transdermal and topical drug delivery expert who was a founder and Chief Executive Officer of MedPharm, a UK-based contract provider of topical and transdermal delivery solutions. This company was partially acquired in 2018 and Dr Muddle remains on the board. He has spent over 30 years in the pharmaceutical industry in the drug delivery area.