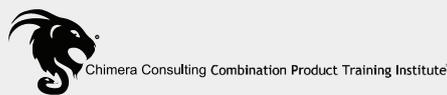


# SKIN DRUG DELIVERY: DERMAL, TRANSDERMAL & MICRONEEDLES



ONdrugDelivery Issue N° 65, March 30th, 2016

## SKIN DRUG DELIVERY: DERMAL, TRANSDERMAL & MICRONEEDLES

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# CONTENTS

4 - 7	<b>New Research Tools for Topical &amp; Transdermal Development</b> Marc Brown, Chief Scientific Officer, Rob Turner, Director of Performance Testing and James Gibbons, Commercial Manager <b>MedPharm</b>
9 - 12	<b>Microbristle Applicator (MBA™) Systems for Topical and Transdermal Drug Application</b> Pierre Michelet, Head of Global Sales Healthcare, Karl Hartstock-Martin, Head of Product Development and Moritz Beyhl, Project Manager <b>GEKA</b>
14 - 16	<b>The Rapid Evolution of the Transdermal Drug Delivery Industry Spawns Innovation</b> Luis Tissone, Director of Life Sciences <b>Trelleborg</b>
18 - 22	<b>Vaccine Delivery Using the Nemaura Solid Dose Injector</b> Joanne Broadhead, Product Development <b>Nemaura Pharma</b> Karmen Cheung, Department of Chemical Engineering <b>Loughborough University</b>
23 - 25	<b>The Criticality of Adhesive Selection for Optimal Transdermal Drug Delivery Systems</b> Megan Greth, Business Manager <b>ARx</b> Gozde Karabiyik, Product Development Scientist <b>Adhesives Research</b>
26 - 30	<b>Optimising In Vitro Testing for Transdermal and Topical Drug Products</b> Tony Copley, Managing Director <b>Copley Scientific</b>
32 - 35	<b>US FDA Issues Guidance on Human Factors Studies for Combination Products</b> Michael Gross, Principal Consultant <b>Chimera Consulting</b> Adam Shames, Chief Executive Officer <b>Core Human Factors</b>



## MICRO BRISTLE APPLICATORS

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- COMBINE DEPOSITION & APPLICATION IN ONE SYSTEM
- INCREASE PRECISION OF APPLICATION
- INCREASE DOSAGE PRECISION WITH SIMPLE SYSTEM
- AVOID THE DRAWBACKS OF CURRENT APPLICATION SYSTEMS
- USE PROVEN KNOW-HOW & TECHNOLOGY WITH PURE PHARMAGRADES PLASTICS

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- For medical applications such as in wound care the entire tube including the brush will be sterilized prior to filling.



NEOPAC  
THE TUBE



## NEW RESEARCH TOOLS FOR TOPICAL & TRANSDERMAL DEVELOPMENT

MedPharm has developed new research tools to de-risk and expedite the development of topical and transdermal products for its clients. These tools also enable companies to assess the delivery of their molecules to their targets better, in what is a growing area of the pharmaceutical sector. In this article, Marc Brown, PhD, Chief Scientific Officer; Rob Turner, PhD, Director of Performance Testing; and James Gibbons, Commercial Manager, all of MedPharm, provide a view on the current topical and transdermal market and elaborate on some of the common approaches to product development in this area. The authors reveal the company's newest model, the MedFlux-HT™ system, which represents a significant step forwards in the field of skin permeation and penetration assessment; a crucial part of the topical and transdermal product development process, increasing data accuracy, detail and throughput.

### GROWTH IN TOPICAL & TRANSDERMAL APPLICATIONS

The topical and transdermal drug delivery market was expected to have reached a size of US\$31.5 billion (£22 billion) in 2015<sup>1</sup> and in recent years there has been an increase in efforts to deliver drugs via these routes. This trend appears to have been driven by a number of factors:

- 2015 saw a continued investment in the field, fuelled by a buoyant, albeit occasionally volatile, investment market. Companies such as Dermira (Menlo Park, CA, US) and Aclaris (Malvern, PA, US) floated on the stock market for values of \$125 million and \$55 million, respectively, both within the last 18 months.<sup>2-3</sup>
- The mergers and acquisitions (M&A) cycle has continued with Kythera (Westlake Village, CA, US) being acquired by Allergan which, in turn, has been acquired by Pfizer thus creating

the world's largest drug developer. One effect of this cycle has been an increase in funds flowing into smaller dermatology companies from increased investor confidence that has led to an increase in product development.

- A number of higher value dermatology products will come off patent in the years ahead, and these include Taclonex (betamethasone and calcipotriene), Picato (ingenol mebutate) and Elidel (Pimecrolimus).<sup>4</sup> This, combined with a perceived logical adaptability of the regulations created for demonstrating equivalence, particularly in Europe, has encouraged a number of high profile generics companies to grow their portfolio in the dermatology sector.
- Finally, as companies look to bolster their pipelines in the face of patent cliffs or M&A activity, there are a number of companies that are refocusing on the dermatology markets, including Almirall and Novartis. GlaxoSmithKline has decided to continue its commitment to



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dermatology, with four programmes in early clinical development.<sup>5</sup> Other companies hope to take advantage of the benefits of delivering therapeutics either topically or transdermally. These benefits include enhanced patient compliance, product life cycle management, brand line extension and avoidance of first pass metabolism.

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“The current trend among new compounds being developed is that of increasing lipophilicity... yet lipophilic molecules are more challenging to deliver into or across the skin, necessitating the screening of candidates in human skin and making formulation development and optimisation even more important.”

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MedPharm, a leader in topical and transdermal formulation development, testing and manufacturing, has developed a new battery of testing and development tools. These tools offer a previously unattainable level of accuracy, speed, efficiency and reliability, enabling MedPharm’s clients to make informed decisions about their projects and giving them confidence in the performance of their products. In the recent past, MedPharm has used these models as a crucial part of a development strategy that ultimately achieved biowaivers for two generic products in the EU, the first time this has happened for topical products of this type.

#### CURRENT GOLD STANDARD

There is a large number of factors that are taken into consideration when developing and testing topical and transdermal products. Once the process of developing and optimising a formulation that is fit-for-purpose has commenced – a process worthy of an article in its own right – there are several testing models considered essential to the development process.

For both topical and transdermal drug product development, the primary challenge

of delivery is overcoming the intrinsic barrier properties of the skin. Before a medication is tested to ensure it will reach its target, it is important to test that the drug is released from a formulation. In topical and transdermal products this is achieved through *in vitro* release testing (IVRT).

Data from IVRT is increasingly sought by regulators to provide an understanding of product performance and quality. Such information is often requested at certain time-points during stability studies to show that drug release is the same throughout a product’s shelf life.<sup>6</sup> However, drug delivery to and across the skin is a complex process and it is not enough just to show that the drug releases from a formulation.

Skin permeation and penetration studies are a key aspect of almost all topical and transdermal product development programmes. From an early stage it is important to select the right molecule for the job. The ideal compounds are thought to be within a certain molecular weight (<500 Da) and moderately lipophilic (logP(octanol/water) 1-3.5).<sup>7</sup> However, there are always exceptions to these rules, thus it is important that a well characterised system is used to assess topical and transdermal delivery. MedPharm has built expertise over the years in formulating and delivering challenging molecules with properties often significantly outside of these indicated ranges. Whilst these parameters can be used to make an initial *in silico* approximate ranking of candidates, additional experimental work is necessary to verify candidate validity as *in silico* models cannot fully replicate *in vivo* complexities.

The current trend among new compounds being developed is that of increasing lipophilicity (log P >3) and greater potency. Yet lipophilic molecules are more challenging to deliver into or across the skin, necessitating the screening of candidates in human skin and making formulation development and optimisation even more important. Once a number of candidate formulations are developed, skin permeation studies can give confidence that a drug is reaching targeted areas within the skin or the systemic circulation. Skin permeation and penetration studies should be performed on *ex vivo* human tissue.

The penetration and permeation model is a well-validated tool for the study of percutaneous absorption and determination of the pharmacokinetics of topically applied drugs. The model uses excised human skin mounted in specially designed diffusion

chambers (static or flow-through) that allow the skin to be maintained at a temperature and humidity that match *in vivo* conditions. The formulation is applied to the surface of the skin and the permeation of the compound is measured by monitoring the rate of permeation into the receiver solution underneath the skin samples. This model also allows the drug and metabolites within the different layers of the skin (i.e. epidermis and/or dermis) to be quantified. It is vital to have a permeation and penetration model that offers good control over the potential variables in topical application such as dosing volumes, humidity, temperature and skin thickness.<sup>8-9</sup>

#### Franz Cell

There are several commercially available diffusion cells that can be used for these *ex vivo* skin penetration and permeation studies. The most common is a static cell, known as a “Franz cell” (Figure 1), where a fixed volume of receiver fluid lies directly beneath the skin or other tissue and serves as a reservoir to collect drug that permeates through the skin. The receiver fluid is then assayed at certain time-points so that drug flux across skin can be quantified. If systemic delivery is not the aim, drug penetration within the skin layers can also be quantified.

---

“MedFlux-HT is a continuous flow system with a carefully designed flow-path to enhance local clearance of the receiver fluid from beneath human skin. This design allows the user to generate more accurate and more detailed flux profiles within a shorter time frame.”

---

The fixed volume of the Franz cell can cause issues when studying compounds that are highly lipophilic (logP>4). This is because lipophilic compounds are insoluble in the physiological, aqueous-based receiver fluid. In these situations additives such as ethanol, solvents or albumin need to be added to the receiver fluid to allow the drug to partition into the receiver fluid (known as ensuring

“sink” conditions). These solubilisers can artificially modify the barrier properties of the skin and also cause problems when the receiver fluid is assayed by analytical equipment. Unwanted artefacts in the data can occur when solvents migrate from the receiver fluid into the skin and dissolve or breakdown structures such that then leech back into the receiver fluid, contaminating it.

A balance must be struck to ensure the right sink, whilst limiting the potential artefacts in the analytical data. These static cells also require manual sampling making automation and high throughput of samples challenging, if not impossible.

### Flow-Through Diffusion Cell

A second type of commercially available diffusion cell is the flow-through diffusion cell. This system incorporates a receiver fluid that is constantly perfused under the skin using peristaltic pumps. These systems can be advantageous as they address some of the permeability challenges of assaying lipophilic molecules static Franz cells. However, these cells have a low flow rate, and the receiver fluid ultimately can collect in a large well under the skin. This can result in a thin, undisturbed layer of static receiver fluid directly under the skin, which limits the partitioning of lipophilic drugs from the skin into the receiver fluid. The net result is that the compound will remain in the tissue, accumulate and not partition into the receiver fluid. In this situation, flux calculations are not possible making comparison of vehicles difficult.<sup>10-11</sup>

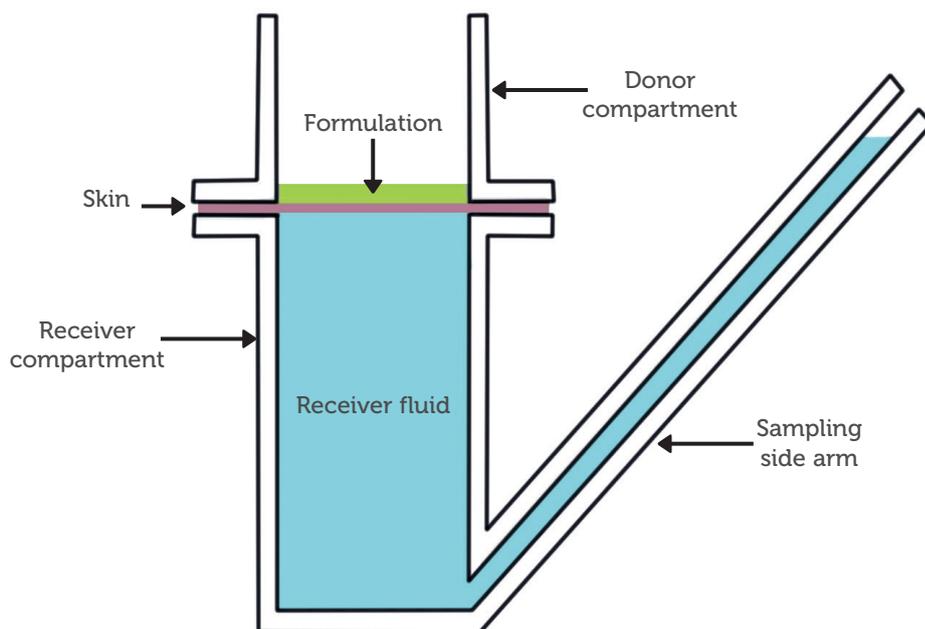
### MEDPHARM'S NEW PERMEATION MODELS

#### MedFlux-HT™

To overcome the limitations of the commercially available diffusion cells, MedPharm’s team of UK and US scientists have developed a proprietary system to assess skin and tissue permeation and penetration; the MedFlux-HT system (Figure 1). By leveraging MedPharm’s years of experience in developing and testing topical and transdermal formulations, this new system generates more valuable data on the performance characteristics of topical and transdermal vehicles.

MedFlux-HT is a continuous flow system with a carefully designed flow-path to enhance local clearance of the receiver fluid from beneath human skin. This design allows the user to generate more

### MedPharm’s Static Franz Cell



### MedPharm’s MedFlux-HT™ Cell

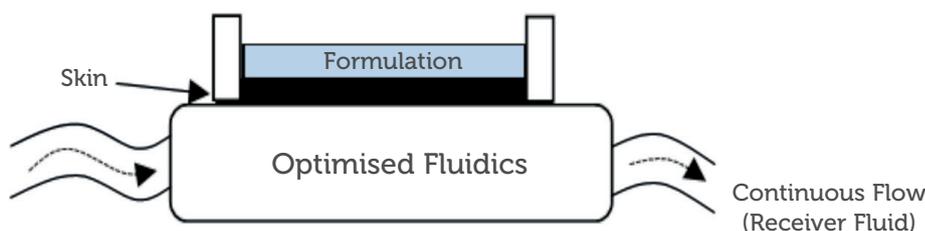


Figure 1: Schematic representation of a static Franz cell (top) and MedFlux-HT™ cell (bottom).

MedPharm’s Static Franz Cell	MedPharm’s MedFlux-HT System
<ul style="list-style-type: none"> <li>• Widely used in the industry</li> <li>• Manual sample collection</li> <li>• Static system</li> <li>• Receiver fluid may have to include additives to ensure sink conditions</li> <li>• Meets IVRT /SUPAC criteria</li> <li>• Ideal for skin penetration studies</li> <li>• Larger dosing areas allows increased exposure of the skin to the formulation</li> <li>• Ideal for regulatory submissions</li> <li>• Study duration 6-8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• MedPharm’s proprietary high-throughput system</li> <li>• Automated sample collection</li> <li>• Flow-through design with rapid local clearance</li> <li>• Sink conditions easily achieved with biologically relevant receiver fluid</li> <li>• Ideal for skin permeation studies</li> <li>• More accurate permeation profiles and fluxes over more data points</li> <li>• Smaller dosing area allows larger formulation screens</li> <li>• Ideal for early development and screening</li> <li>• Study duration 2-3 weeks</li> </ul>

Table 1: Comparison of the different permeation and penetration systems available at MedPharm.

accurate and more detailed flux profiles within a shorter time frame. The increased local clearance from beneath the skin and optimised receiver fluid flow improves sink conditions and facilitates the analysis of lipophilic compounds, eliminating the need for the additives to be present in the receiving fluid. In addition, MedFlux-HT has been engineered with a high-throughput approach to sample collection and analysis in mind. The system is thermostatically controlled so as to maintain constant physiological temperature and the collection of the receiving fluid is automated for higher throughput sample quantification.

The MedFlux-HT system has also been designed specifically to minimise the amount of skin required for dosing. This has the benefit of increasing the repetitions that can be achieved with an often limited tissue supply. A full comparison of permeation and penetration systems is provided in Table 1.

#### Additional Models

As the leader in field, MedPharm has developed a number of other performance testing models which it uses to assess a variety of formulation and drug characteristics in order to allow its clients to make more informed decisions. These include models to assess drug metabolism in the skin, as well as assays to assess drug binding within the skin.

MedPharm possesses a battery of *ex vivo* human skin efficacy models where, for example, fungal, bacterial and viral skin infections can be replicated. Such systems represent the closest model to the actual disease itself where drug delivery and formulation efficacy can be evaluated and compared without having to perform clinical trials. This provides the ideal opportunity to de-risk the product development process. In addition, these models have been recognised

as validated by the regulatory authorities for use in the assessment of therapeutic bioequivalence.

Further, MedPharm's proprietary skin inflammation models can assess corrosivity and irritation under OECD guidelines 431 and 439, which can all provide a strong indication as to a formulation's viability for the intended target indication and toxicity before programmes progress to the clinic.

#### CONCLUSIONS

There are a number of challenges that are associated with developing topical and transdermal medications. MedPharm has the expertise to assist in all aspects of the process, from molecule selection through formulation development, testing and clinical trial material manufacture. MedPharm constantly strives to develop new, insightful tools that allow its clients to make informed decisions enabling them to ultimately develop the best product.

The MedFlux-HT system offers more detailed, more accurate as well as higher throughput data generation which, in tandem with MedPharm's other proprietary models, can facilitate quality-by-design approaches for formulation development and thus de-risk the development process by allowing selection of only those formulations with the best efficacy and safety profiles. All of these models are available to MedPharm's clients on a contract service basis together with services in formulation development and GMP manufacturing. The company also develops its own topical and transdermal drug delivery technologies that are available for licensing.

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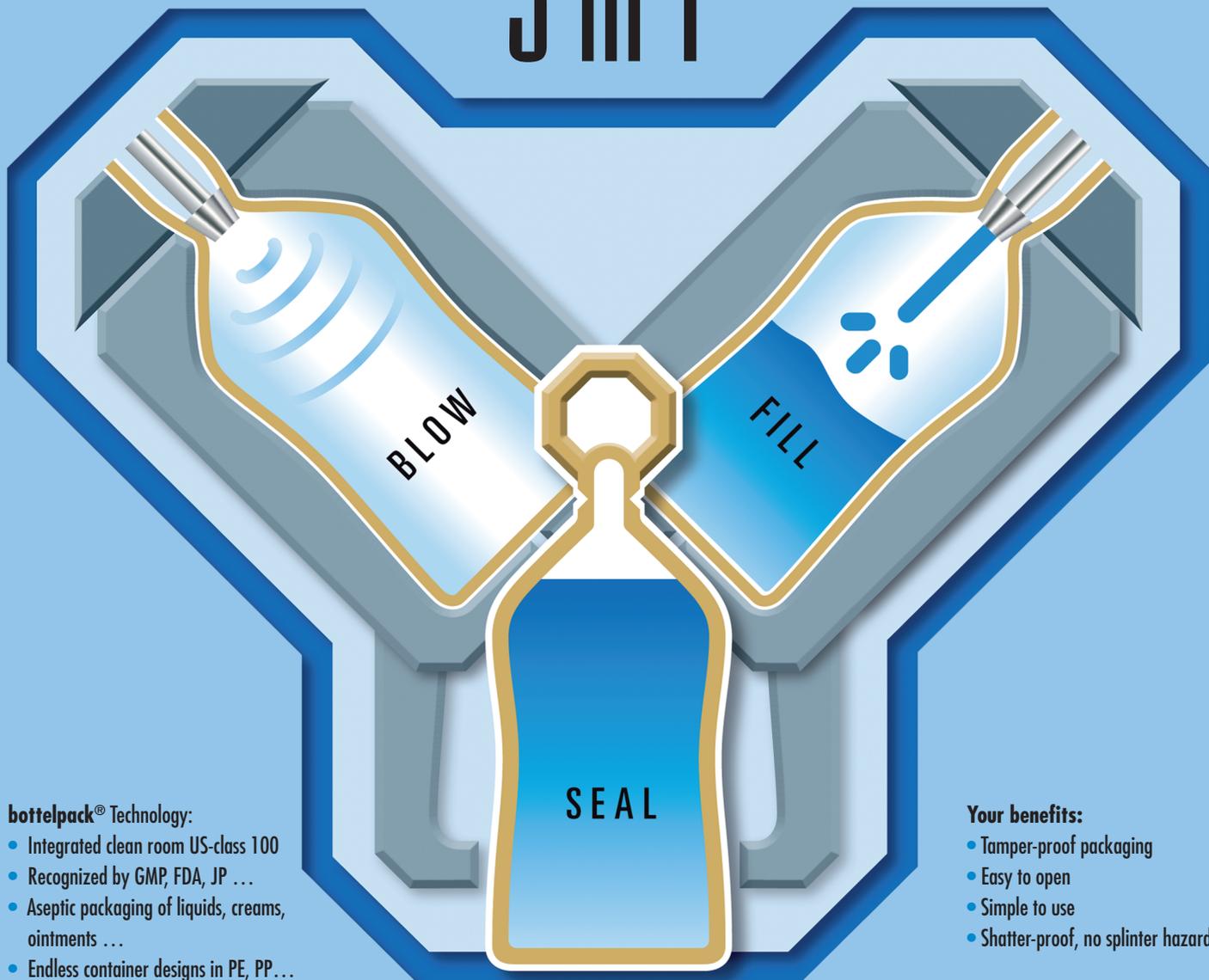
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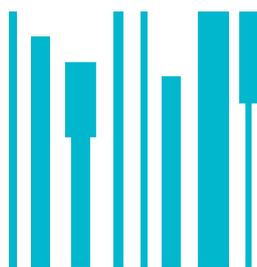
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# GEKA

HEALTHCARE



## MICROBRISTLE APPLICATOR (MBA™) SYSTEMS FOR TOPICAL AND TRANSDERMAL DRUG APPLICATION

In this article, Pierre Michelet, Head of Global Sales, Healthcare; Karl Hartstock-Martin, Head of Product Development; and Moritz Beyhl, Project Manager, all of GEKA, present the innovative technology of microbristle applicators (MBA™) for a more precise and hygienic application within topical and transdermal treatment. MBA™ comprises a platform of moulded, pure plastic applicators with very fine bristles to apply liquid and semi-liquid formulations.

### IMPROVEMENT IN TOPICAL & TRANSDERMAL APPLICATION

Patients can today easily find deposition systems for liquid and semi-liquid drugs, but they face a real lack of suitable application systems for these formulations, in particular if looking for precise and hygienic dosing with pharma-applicators.

This is even more the case when a combined deposition and application is required. Current application systems like cotton tips, flocked applicators, spatulas, nail polish brushes or fingers present major drawbacks such as a lack of sterility, application and dosage precision, poor hygiene and fibre detachment.

Therefore, GEKA has adapted its proven technology used in cosmetics to provide systems that combine these two attributes to fulfil pharmaceutical and cosmetic needs. The systems use applicators with extremely delicate microbristles (Figure 1), resulting from many years of expertise in injection-moulding technology and patented processes (EP1465759B1, Method And Device Of The Production Of Brushes). These applicators allow users to uptake formulations under

hygienic conditions and to apply these with high precision – even for the most sensitive and pinpoint application areas. As just targeted areas will be touched with the very fine bristles, an increased efficiency and reduced side effects of application are the result.

### CONTRIBUTION TO INCREASED COMPLIANCE & PERFORMANCE

The benefits of microbristle applicators are:

#### 1. Increased application precision (Figure 2):

- Track precision: bristles do not spread, but create a precise, continuous track
- Dot precision: bristles do not spread, but create a precise dot
- Targeted areas: MBA™ reach several areas with their adjusted rigidity and perfect resilience.

#### 2. Increased dosage precision:

The MBA™ technology and expertise in topography/design allows us to design applicators with specific shape and geometry for a defined load and release dose of the drug in a consistent and patient-independent way.



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“These applicators allow users to uptake formulations under hygienic conditions and to apply these with high precision – even for the most sensitive and pinpoint application areas.”

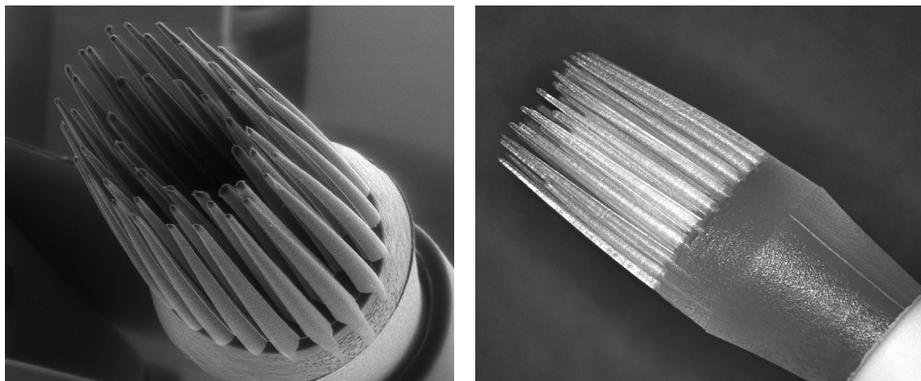


Figure 1: Microscopic view of microbristle applicators.

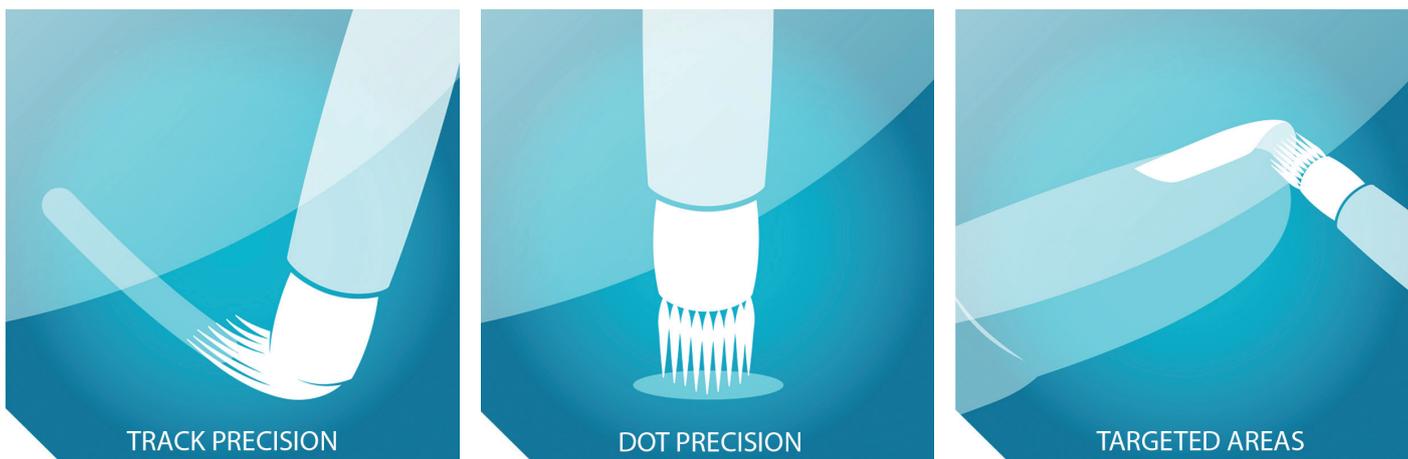


Figure 2: Increased application precision provided by track, dot and targeted areas.



Figure 3: Microbristle applicators for dentistry, skin care and prostaglandin analogs.

**3. Guarantee of purity and hygiene:**

- Pure pharma-grade plastics (e.g. LDPE) are used for production without additives, glues, metal or loose fibers.
- Automated production in one step
- Radio sterilisation at 25 kGy
- Depending on the design of the customised MBA™, a wide range of materials (polyolefin and TPE) can be offered.

**4. Guarantee of traceability:**

Full traceability up to the raw materials is ensured.

Microbristle systems are not limited to a specific application field and can be used for various market segments (as shown in Figure 3) such as:

- Dermal care (Rx medicated skin care dermatology, OTC skin care, cosmetic skin care)
- Oral health care, e.g. mucus membrane treatment, aphthae
- Dentistry, e.g. easing dentists’ gestures
- Dental for patients, e.g. bleaching treatments, interdental brushes
- Eye care, e.g. drops and ointment, infections, sty, lashes/brow treatments

- Hair/scalp treatments
- Animal health
- Ear /nasal /foot /rectal /vaginal care
- Diagnostics.

**TEST METHODS & RESULTS**

GEKA Healthcare can provide services such as sharing methods or realising customised tests using its specifically developed Performance Test Method, for example, to evaluate dosage pick-up and release, or calculation of standard deviation to monitor the consistency of application.

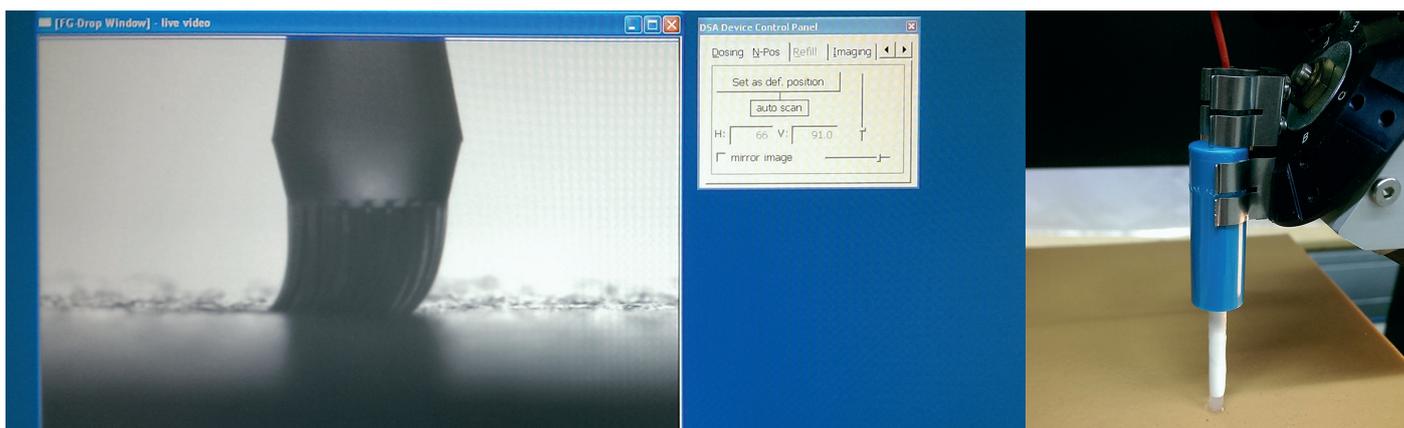


Figure 4: Test system.

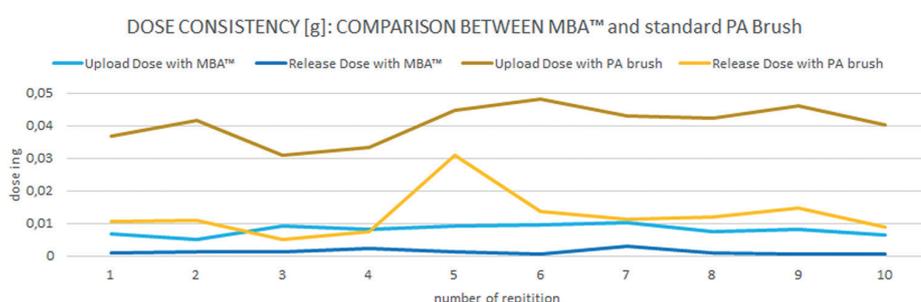


Figure 5: Dose consistency.

Therefore a specific machine with a movement precision of 0.1 mm, included camera system and exact scale is used. This test system was created in collaboration with Ansbach University of Applied Sciences (Figure 4) and allows us to recreate the movement of the applicator during usage by consumer (various positions and angles of the applicator) and to measure uploaded and released quantities of formulations.

**Dosage Precision Increase**

The graph in Figure 5 illustrates the difference between standard polyamide (PA) brushes and the GEKA Healthcare MBA™ for the uploaded dose (dose ‘charged’ on the applicator and ready to be applied on the skin) and for the released dose (dose effectively applied on the skin). The product used is water and the system used is the dip-in applicator 28730.

In conclusion, the difference between uploaded and released quantity is over four times smaller when using an MBA™, rather than the PA brush.

**Dosage Precision Consistency**

Figure 6 illustrates the consistency of dosing for a standard PA brush and for a MBA™ applicator. The product used is water and the system used is the dip-in applicator 28730. The standard deviation is more

than ten times smaller for the released quantity with MBA™ compared with a standard PA brush, which means much higher consistency of dose really applied to the patient. The standard deviation for the uploaded quantity is also much smaller for the MBA™.

**DESIGN & PLATFORM NEEDED FOR A SPECIFIC TRANSDERMAL USE**

**Different designs**

GEKA Healthcare offers MBA™ in different shapes and sizes, for example with 4.7 bristles per mm². Figure 7 shows convex and concave applicators, applicators with reservoir zones and comb-, brush-, and paint-type applicators. Upon test methods, the specific applicator topography is designed to perfectly match the drug characteristics (e.g. viscosity, surface tension). The length of bristles, space between bristles, bristle density, entire wettable surface and the surface tension of the applicator material can be defined.

**Different Platforms**

MBA™ can be combined with various packaging systems as Figure 8 shows:

**a) Dip-in formats with single usage sticks**

The drug is contained in any standard bottle of customer’s choice and the single-

stick applicator will be delivered beside the bottle. The quantity of sticks per patient is to be defined by the pharmaccompany. The patient deposits a drop of drug on the applicator, and then applies it on the target. Once used, the single-usage stick can be thrown away.

**b) Dip-in formats with multi-dose packs**

A complete multi-use packaging is perfectly adapted for warts, scars and wound care. It can contain a small polyethylene terephthalate (PET) or polypropylene (PP) bottle equipped with a wiper ensuring the removal of excess product before the application and a screw-on cap equipped with an MBA™ applicator. The MBA™ can also be combined with temper-evident, child-resistant and standard screw caps with thread according to DIN 168.

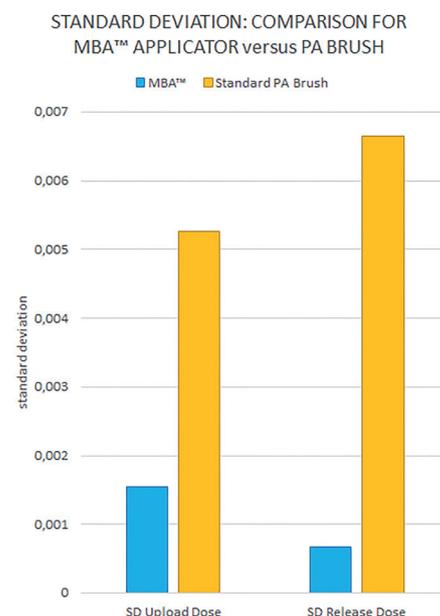


Figure 6: Standard deviation.

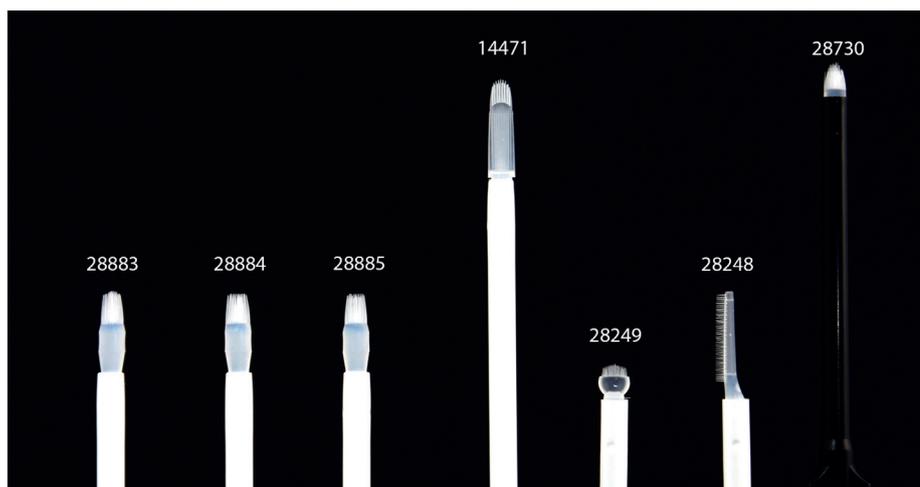


Figure 7: MBA™ types (from l to r): convex, concave, reservoir, flat paint-type, micro, comb, brush type.



Figure 8: MBA™ platforms: (a) dip-in formats with single usage sticks, (b) dip-in formats with multi-dose packs, (c) dip-in single-dose blow fill seal and (d) flow-through tube Twist'n'brush.

c) Dip-in single-dose blow fill seal (BFS) packs Together with rommelag® (Buchs, Switzerland), a cost-efficient alternative to expensive and complicated dosing systems has been developed. BFS bottelpack® containers are aseptically formed, filled and sealed in one operation cycle in a closed environment. The dip-in microbristle applicator is inserted during the BFS process. The convenient, single-dose device allows for an intuitive, simple use combined with hygienic and precise deposition and application. It uses an advanced aseptic BFS process according to US Pharmacopeia, FDA and GMP guidelines.

d) Flow-through tube 'Twist'n'brush' GEKA partnered with Neopac (Oberdiessbach, Switzerland), the packaging specialist for Polyfoil® high barrier tubes, to develop this single-dose tube packaging. It is based on the original Twist'n'use™ closure system with integrated tamper-evident function: when the nozzle is twisted, the internal tamper-evident pin is detached and the liquid or semi-liquid contents can be applied precisely, without being contaminated. The ultra-fine, soft, pharma-grade plastic bristle brush allows a convenient and gentle topical application of the medicinal products,

with utmost precision and hygiene. For medical applications (such as wound care) the entire tube and applicator will be sterilised with gamma rays prior to filling.

In order to fulfil the maximum standards of quality, safety and consistency, GEKA manufactures under strict compliance with the stringent ISO 9001:2008 and applicable GMP guidelines. It guarantees complete traceability of production right down to the raw material. Also ISO 13485 and 15378 are proposed for new developments, as well as the completion of the necessary DMF. A clean room is available (particle limit value according to clean room class 8, ISO 14644) to produce under controlled atmospheric conditions.

### CONCLUSION

GEKA Healthcare shows with its MBA™ technology the answer to the rising trend of precise and hygienic drug application that existing systems aren't able to fulfil. The ability to mould fine structures with pure plastics and the experience in development of applicators and packaging systems allowed GEKA Healthcare to create a platform for precise and consistent drug application. Within this platform, the MBA™, various shapes and designs of applicators are possible. As shown, there are many possibilities of usage and application fields. Whenever a drug or formulation needs to be applied in a precise, consistent and hygienic way, the MBA™ is the answer.

### ABOUT GEKA

Driven by an increasing market demand for innovative solutions improving the way a drug or cosmetic is applied by/to the patient precisely and hygienically, GEKA Healthcare has been created as a division of the GEKA Group.

GEKA is one of the world's leading manufacturer of brushes, applicators and complete packaging systems for cosmetics industries. The know-how and experience in 1K- and 2K-injection micro-moulding was the basis to create unique microbristle applicators (MBA™). This platform of plastic moulded applicators and the development of solutions for precise and hygienic applications is the core competence of GEKA Healthcare.

## ONdrugDelivery 2016/17 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
April 2016	Pulmonary & Nasal Drug Delivery	n/a
May 2016	Injectable Drug Delivery: Devices Focus	April 11th
June 2016	Connected Drug Delivery Systems	May 9th
July 2016	Novel Oral Delivery Systems	June 13th
September 2016	Wearable / High Volume Injectors	August 1st
October 2016	Prefilled Syringes	August 29th
November 2016	Pulmonary & Nasal Delivery	September 26th
December 2016	Delivering Biotherapeutics	October 24th
January 2017	Ophthalmic Drug Delivery	November 21st
February 2017	Prefilled Syringes	December 19th
March 2017	Skin Drug Delivery: Dermal, Transdermal & Microneedles	January 23rd



# TRELLEBORG

## THE RAPID EVOLUTION OF THE TRANSDERMAL DRUG DELIVERY INDUSTRY SPAWNS INNOVATION

Microneedle-based technology is a significant advance in the delivery of vaccines due to its strong stability and greater effectiveness. In this article, Luis Tissone, Director of Life Sciences, Trelleborg, outlines technological developments behind microneedle design including the use of advanced liquid silicone rubber (LSR) and two-component injection technology, and explores the advantages this offers over traditional intramuscular routes.

The transdermal drug delivery market is growing dramatically as a result of the multitude of benefits it provides for administering certain drugs over conventional systems. The rapid evolution of transdermal delivery is especially apparent with microneedle products due to its ability to provide exciting potential improvements for vaccine delivery (Figure 1).

Amongst all the companies involved in developing microneedle products, almost 50% are start-ups receiving support from financial investors. These start-ups, as well as the more established companies such as Pfizer, Roche, Johnson & Johnson, Novartis and Bayer, are looking at all the ways they can gain a competitive advantage. To ensure optimal performance, such companies are taking into consideration all the components used in their microneedle delivery system design. Knowledge of advanced technologies is crucial (Figure 2).

### MICRONEEDLE PATCH TYPES & MARKET GROWTH

Advanced liquid silicone rubber (LSR) and two-component injection technology can accelerate the development of transdermal drug delivery devices such as microneedle

“Many new studies show that microneedle use for vaccination delivery reveals either comparable or greater immunogenicity, a stronger level of stability and more advantageous dose sparing as compared to the traditional intramuscular routes.”

patches. There are four types of microneedles currently on the market. First is the hollow microneedle, which only requires a liquid drug formulation to be infused through the bores. The solid microneedle punctures holes in the skin where a patch can then be applied. Then there is the dissolving microneedle that is coated with the drug. Lastly, there are polymer microneedles that are made from special polymers offering dissolving, non-dissolving or hydrogel-forming options.

All of these microneedle patch types offer an excellent delivery route to enhance



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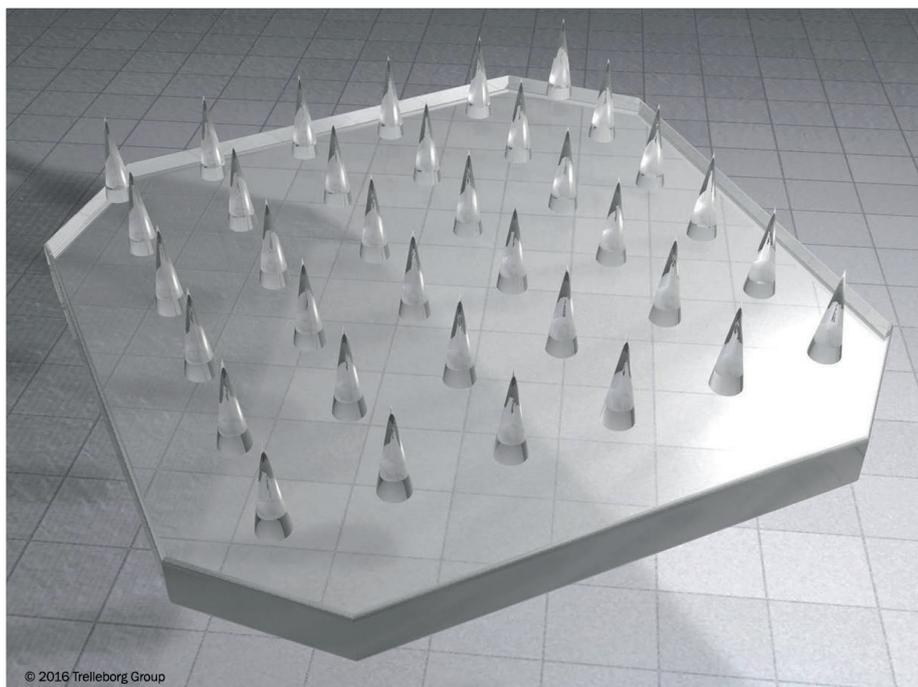


Figure 1: A detail of a transdermal patch using microneedles.

the vaccination's effectiveness. This is primarily because microneedles possess the ability to target the rich network of immunologic antigen-presenting cells in the dermis and epidermis layers under the skin. Many new studies show that microneedle use for vaccination delivery reveals either comparable or greater immunogenicity, a stronger level of stability and more advantageous dose sparing as compared with the traditional intramuscular routes.

#### VERSATILE LSR TECHNOLOGY FOR MICRONEEDLE COMPONENTS

Advanced technologies are coming into play in enhancing microneedle components during the design process. For example, product developers and research institutes are looking at the use of LSR technology to enhance the performance of their transdermal delivery systems.

Silicone – and LSR in particular – is becoming an increasingly attractive choice of polymer due to a number of advantages. Silicone is well regarded for its favourable haptic properties and proven generally not to cause skin irritation. In addition, silicone provides biocompatibility and compliance with relevant industry regulations. Most importantly, LSR offers fast, essentially unlimited, processing possibilities for the most complex high-precision technical components in large volumes (Figure 3).

LSR technology is very effective where:



Figure 2: One of Trelleborg's Class 8 cleanrooms where safety-critical medical LSR components are produced fully automatically to a zero-defect policy.

- Customised solutions are needed
- Components with extremely complex, thin, or tiny features are needed, such as a carrier or protective element as part of a microneedle patch
- Multiple materials or layers of materials need to be combined into a composite structure
- The surface texturing and surface enhancements of devices are critical to provide the intended absorption of medicine through the skin
- The highest component precision and consistency of quality are key to provide best possible support to human health.

“Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. It may provide enhanced therapeutic profiles for therapeutics and vaccines.”



Examples of micro LSR and two-component parts produced by Trelleborg (ladybird shown for scale).

Advancements in drug delivery systems will be the result of access to newly developed materials, emerging methods of technological delivery and advances in manufacturing capabilities. This is precisely what LSR injection technology is offering. LSR technology can deliver smaller, more robust and stronger polymers to provide more stability, wear and usage. The more demanding requirements of pharmaceutical companies and device manufacturers have led to a more concentrated effort to deliver breakthroughs in LSR technology and microfabrication. This necessitates incorporating the smallest of parts, down to micro- and already nano-gram weights (Figure 4).

#### MULTIPLE FABRICATION METHODS & USES

Microfabrication manufacturing technology can be of help in delivering innovative microneedle designs. To fully understand microfabrication, it is important first to note that microneedles consist of a plurality of micro-projections, generally ranging from 25–2000  $\mu\text{m}$  in height, of different shapes, which are attached to a base support. There are numerous configurations that can compose a microneedle patch. The flexibility of LSR can assist in achieving those configurations regardless of complexity.

The first microneedle devices were fabricated from silicone but many other materials have also been used in its

fabrication; stainless steel, dextrin, glass, ceramic, maltose, galactose and various polymers, for example.

In recent years, manufacturing of microneedles has encompassed conventional microelectronic fabrication technologies,



Figure 4: AQL inspection of micro parts in a Class 7 cleanroom environment.

including chemical isotropic etching, injection moulding, reactive-ion etching, surface/bulk micromachining, polysilicon micro-moulding, lithography-electroforming-

replication, and laser drilling. Microneedles have been fabricated with a wide range of designs (different sizes and shapes) and different types (solid, hollow, sharp or flat).

#### MARKET PROJECTIONS

With silicone and polymer compounds falling within our core area of expertise, the opportunities to enhance transdermal delivery system design is indeed an exciting one. Device manufacturers are investing in R&D and design strategies to support the transdermal drug delivery industry, valued at US\$13.5 billion (£9.5 billion) in 2013 and expected to reach \$21.7 billion by 2018, according to MicroMarketMonitor (Pune, India).

Microneedles are not limited to any specific class of drugs. According to a 2014 Roots Analysis report, “Microneedles for Transdermal and Intradermal Drug Delivery, 2014-2030”, more than 70% of the products in development are patches incorporating solid or dissolvable needles, while the rest are hollow microneedle arrays that employ the use of a syringe. With several new microneedle-based therapeutic product launches expected by the end of this decade, the report concludes that the overall market for microneedle-based delivery devices will reach annual sales of 485 million units by 2030.

#### LEVERAGING A COMPETITIVE ADVANTAGE

Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. It may provide enhanced therapeutic profiles for therapeutics and vaccines. It allows for the administration of lower levels of drug to achieve the same therapeutic endpoints.

Additionally, microneedles provide an alternative to traditional needles. This industry provides a means to overcome one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination. The variation in the microneedle types could also prove useful in controlling the kinetics of vaccine release. Such complex variations will further support the use of LSR technology and will be instrumental in the further evolution in the effectiveness and use of transdermal delivery systems.

# MICRONEEDLES 2016

4th International Conference on Microneedles

23 - 25th May 2016 at GSK House, London

Last chance to register

Graphic: Gary Meek/Georgia Tech

**The International Conference on Microneedles provides a unique international forum for academics and industry involved in the design, development, application and clinical translation of microneedle technology. The conference includes keynote presentations from leaders in the field interspersed with poster sessions and numerous opportunities for networking, when researchers at all levels can interact.**

The event will take place at GSK House in London from 23-25<sup>th</sup> May. Registration includes access to both the Conference and Exhibition in addition to the Gala dinner event.

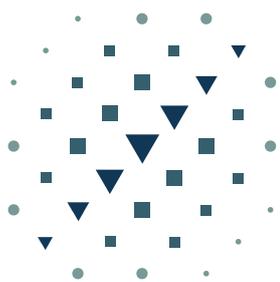
**Registration closes on 11<sup>th</sup> April 2016** and spaces are limited – register now to avoid disappointment.

For more information please visit [www.microneedles2016.org](http://www.microneedles2016.org) or contact the organizers at [contact@microneedles2016.org](mailto:contact@microneedles2016.org).



[www.microneedles2016.org](http://www.microneedles2016.org)





nemaura  
pharma

## VACCINE DELIVERY USING THE NEMAURA SOLID DOSE INJECTOR

In this article, Joanne Broadhead, PhD, Product Development, Nemaura Pharma; and Karmen Cheung, MSc, Department of Chemical Engineering, Loughborough University, UK, report an investigation into the delivery of two vaccines using Nemaura's solid-dose injection technology.

Vaccines are widely recognised as one of the greatest achievements in public health, yet incorrect handling and administration can compromise their effectiveness. The process of storage, handling, preparation and

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"As an alternative to the microneedle concept, Nemaura has developed a novel solid dose injector device which enables the controlled delivery of solid dose vaccine formulations."

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administration can be complex, particularly where vaccines are being distributed in developing countries in which security of the cold chain can be difficult to assure. In addition, administration procedures can be a source of error.

For conventional vaccines supplied in vials, there can be contamination and stability risks associated with the advance preparation of syringes ("pre-drawing"). This is why the US Centers for Disease Control & Prevention (CDC) encourages the use of unit dose, ready to administer vaccines.<sup>1</sup>

It is clear even from the brief discussion above that a vaccine which does not require cold-chain handling and which is single use, unit dose and ready to use, requiring no specialised training to administer, would offer a significant step forwards in maximising the benefits of vaccination.

Microneedle delivery systems have been extensively investigated as a means to address this unmet clinical need. Both removable and biodegradable systems have been evaluated.<sup>2</sup> The former were associated with safety concerns because of the perceived risk of needles fracturing and remaining in the skin. This led to greater interest in biodegradable systems. However, these present significant challenges, particularly in terms of their fabrication.<sup>2</sup>

As an alternative to the microneedle concept, Nemaura has developed a novel solid dose injector device which enables the controlled delivery of solid dose vaccine formulations. This offers similar advantages to microneedle systems in terms of avoidance of cold chain and simplicity of use but, due to its larger size, presents fewer fabrication challenges. In the context of vaccine administration, where only one (or a few) doses are required, the larger size is not considered limiting. Here we present the results of a proof of concept study in mice in which

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Figure 1: Prototype Nemaura solid dose delivery device.

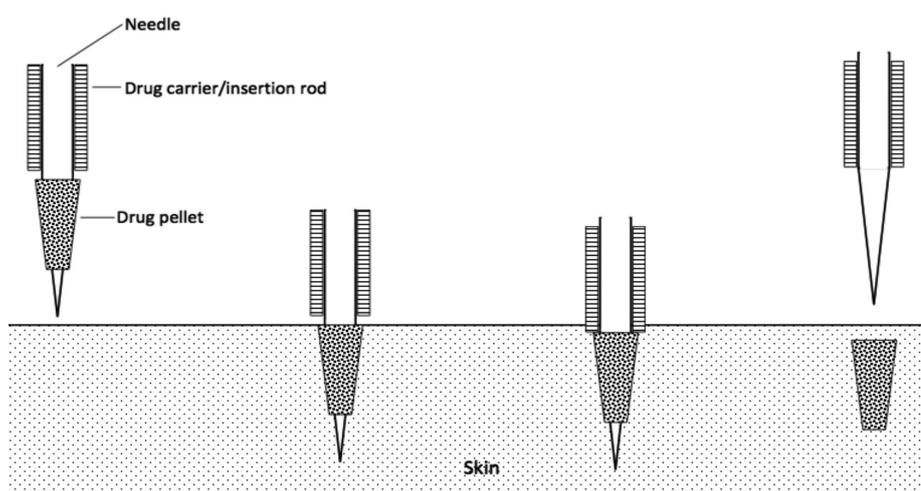


Figure 2: Delivery using the Nemaura solid dose delivery system. Needle is inserted into the skin to the desired depth, pellet accompanies needle into the skin then needle is removed leaving the solid micro-dose formulation inside the skin.

a prototype device was used to deliver a tetanus vaccine and a diphtheria, tetanus and pertussis (DTaP) vaccine.

### NEMAURA SOLID DOSE DELIVERY DEVICE

Figure 1 shows a prototype version of the Nemaura solid dose delivery device. The principle is based upon the initial insertion of a super sharp stainless steel needle to breach the tough outer barrier of the skin followed by delivery of the solid dose formulation in pellet form which is inserted alongside the needle. The needle is subsequently retracted leaving the solid dose formulation in the skin (Figure 2). In this particular prototype, a frustoconical-shaped pellet was used but various pellet geometries are feasible.

The device design can be adapted to allow the solid-dose formulation to be inserted efficiently into the skin either intradermally or subcutaneously depending on the dosing requirements. The device is designed to be easy to administer and includes safety features such as the complete retraction of the needle into the device following insertion of the solid-dose pellet, thus reducing the risk of needlestick injuries.

### IN VIVO PROOF-OF-CONCEPT STUDY

A proof-of-concept study in mice provided a preliminary evaluation of the immunogenicity of the solid-dose vaccine using a Nemaura prototype solid-dose injector.

“The study reported here is an encouraging step forward in developing a vaccine delivery system which is straightforward to manufacture, a low-cost disposable system, easy to use and avoids the problems associated with cold-chain delivery of vaccines, and potentially other biologics.”

### MATERIALS

Tetanus vaccine was selected for one arm of the study. Freeze-dried inactivated tetanus toxoid was purchased from the National Institute for Biological Standards and Control (NIBSC; Potters Bar, UK).

Infanrix® vaccine (sourced from GSK) was used for the DTaP arms of the study. The DTaP vaccine contains tetanus toxoid, pertussis and diphtheria and is a component of the childhood vaccination programme. This vaccine is supplied as a liquid and was converted to a dry state by freeze-drying with suitable excipients. Pharmacopoeia-grade excipients were obtained from reputable excipient suppliers.

### METHODS

#### Manufacture & Characterisation of Pellets

An optimised excipient blend was developed which, when compressed, resulted in pellets with physical properties in the desirable range. Excipients were selected based on their suitability for use in parenteral products.

Freeze-dried vaccine formulations were incorporated into the optimised excipient blend using geometric mixing. The solid-dose formulations were individually compressed into pellets using a bespoke direct compression micro-press. The pellets had a base diameter of 1.6 mm, a tip diameter of 0.8 mm and a height of 2 mm (approximate dimensions). The average mass was approximately 4 mg. Compressed solid-dose pellets were mounted on the prototype device and packaged in a nitrogen environment using a moisture-impermeable barrier material.

Solid Dose Pellet Formulation	Test Conducted	
	Hardness (N) (SD)	Disintegration (seconds) (SD)
High Dose Tetanus Pellet	6.44 (0.68)	27.5 (5.24)
Low Dose Tetanus Pellet	No data <sup>1</sup>	No data <sup>1</sup>
Placebo Pellet	No data <sup>1</sup>	53.0 (7.86)
DTaP Formulation One	7.88 (1.82)	49.0 (19.70)
DTaP Formulation Two	6.48 (1.78)	96.0 (21.63)

Table 1: Hardness and disintegration data.

Test Conducted	Time point (weeks) at temperatures				
	25°C			40°C	
	0	2	4	2	4
Hardness (N)(SD)	6.21 (1.25)	4.59 (1.06)	5.32 (1.06)	3.13 (0.61)	5.04 (1.53)
Disintegration (seconds) (SD)	75.67 (15.16)	Not tested	54.67 (2.66)	Not tested	55.4 (2.41)

Table 2: Hardness and disintegration stability data.

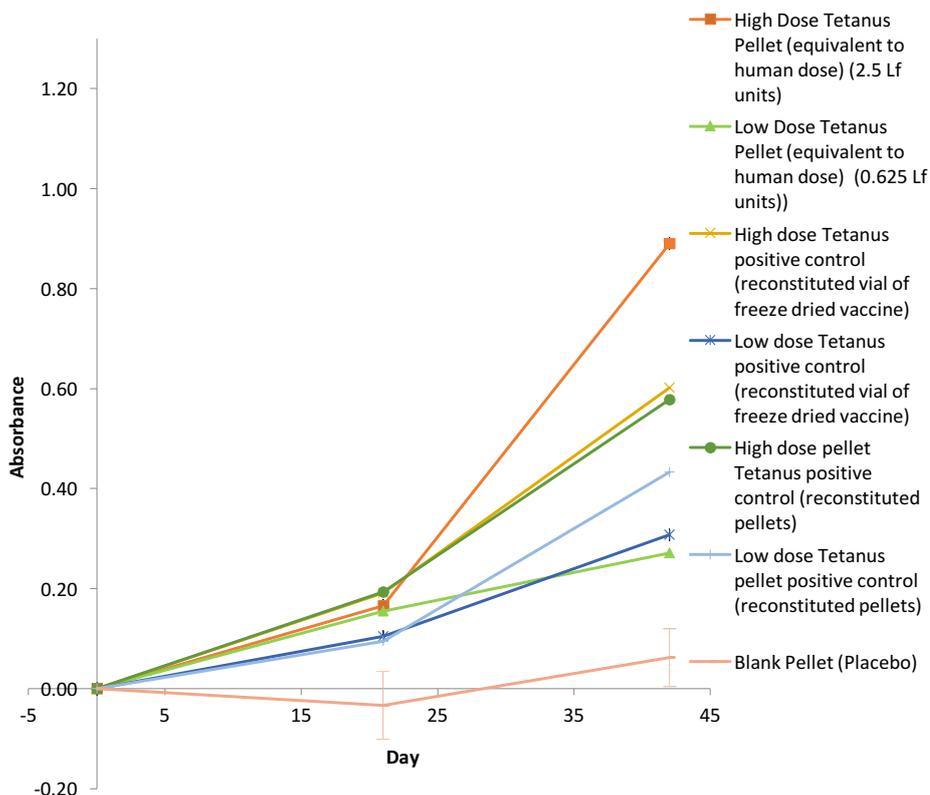


Figure 3: Tetanus immune response (Tetanus Study).

Tetanus pellets were formulated at a “high” dose (2.5 Lf units, equivalent to ¼ of a human dose) and a “low” dose (0.625 Lf units). Relatively high doses were selected because of the lack of adjuvant in the tetanus formulations.

DTaP pellets contained all the components of the original Infanrix<sup>®</sup> vaccine including the adjuvant. Two different freeze-dried formulations, containing different stabilisers, were used in the manufacture of the pellets. Pellets contained approximately 2% of the normal human dose of all components.

Pellet hardness was evaluated using a MultiTest 2.5-i compression instrument (Mecmesin, Slinfold, UK). Friability was evaluated using an in-house friability tester and disintegration time was determined by measuring the time taken for an individual pellet to disintegrate in 1 ml of water.

#### Immunogenicity Study

The immunogenicity study was conducted at a third-party CRO site. For tetanus arms, pellets were administered to ten mice in each dose group. For DTaP arms, 20 mice per dose group were used as each mouse could only provide sufficient serum for two ELISA assays.

Control groups for the tetanus study were administered reconstituted pellets or an equivalent dose of reconstituted, freeze-dried tetanus toxoid as supplied from NIBSC. Control groups for the DTaP study were administered an equivalent dose of reconstituted freeze-dried vaccine or an equivalent dose of Infanrix<sup>®</sup>. A constant dosing volume of 500 µL was used for all control groups. Animals were dosed on day 0 (prime) and day 28 (boost). Blood samples were taken on days 21 and 42.

The pellets were inserted into the skin of the lower back of the mouse in a lateral direction to ensure the pellet was administered subcutaneously. Daily physical and general behaviour of the mice throughout the study was monitored including weight, faecal matter and general movement. Body weight and feed intake of all the animals was evaluated weekly. No mortalities occurred during the study.

ELISA kits (GenAsia Biotech, Shanghai, China) were used to determine the antibody response to the administered vaccine solid dose pellets. Samples from all test animals except the naïve (untreated) control group were diluted five-fold prior to assay. The ELISA assays were performed according to kit instructions.

## RESULTS

### Physical Properties of Pellets

Hardness and disintegration data for sample pellets are shown in Table 1. Previous Nemaura data indicated that a hardness of 3N was sufficient for skin penetration. All tested pellets were sufficiently hard and disintegrated rapidly. Only one pellet was noted to break during the course of the immunogenicity study.

Table 2 provides physical stability data for pellets stored at 25°C and 40°C. Friability testing was also performed and less than 3% weight loss was observed for all tested pellets. This study was conducted using the DTaP Formulation Two pellets and provided assurance that the pellets were sufficiently robust to withstand storage and shipping conditions.

### Animal Observations

Basic observations of the animals were determined to be normal. No mortality occurred and the weight gain of the mice was normal. Minor observations of erythema and oedema were noted at the injection site.

#### a) Immunogenicity: Tetanus Study

Figure 3 shows the anti-tetanus immune response. The results are expressed as an optical density value and are adjusted for the negative control (naïve mouse). Values for blanks, positive and negative assay controls were very similar at both 21 and 42 days enabling the 21- and 42-day data to be directly compared.

The results clearly show that there is an increased effect at day 42 compared with day 21 with all the high-dose groups showing a stronger response than the low-dose groups. The high-dose tetanus pellet gave a stronger response than both positive controls (reconstituted pellets and reconstituted freeze-dried vaccine) which could suggest a dose-sparing effect associated with the solid formulation. However, further studies are required to evaluate this further. All dose groups show a clear response compared with the placebo group.

#### b) Immunogenicity: DTaP Study

Figures 4 to 7 show the immune responses to the DTaP pellets. As for the tetanus study, the results are expressed as an optical density value and are adjusted for the negative control.

The anti-tetanus signal was weaker for the triple vaccine compared with the tetanus

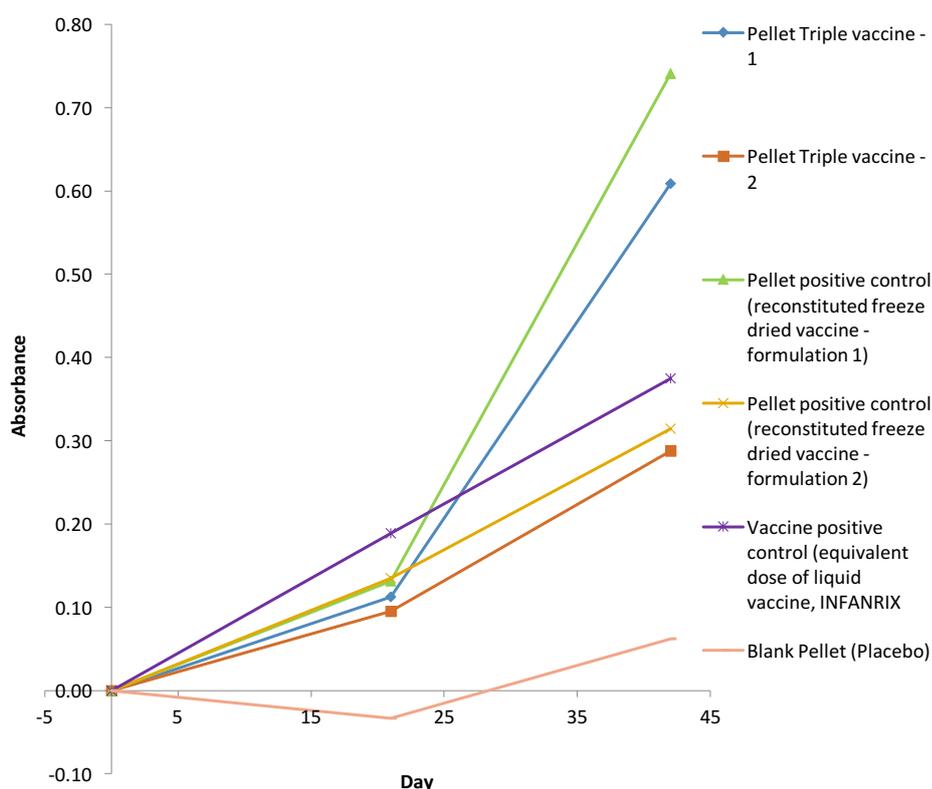


Figure 4: Tetanus immune response (DTaP Study).

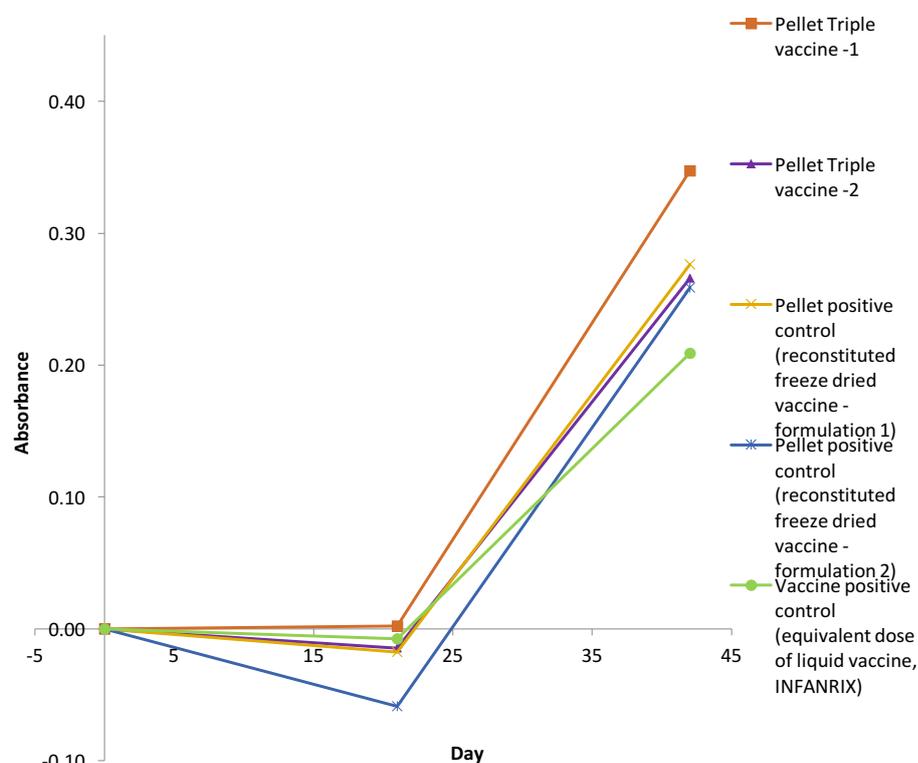


Figure 5: Diphtheria immune response (DTaP Study).

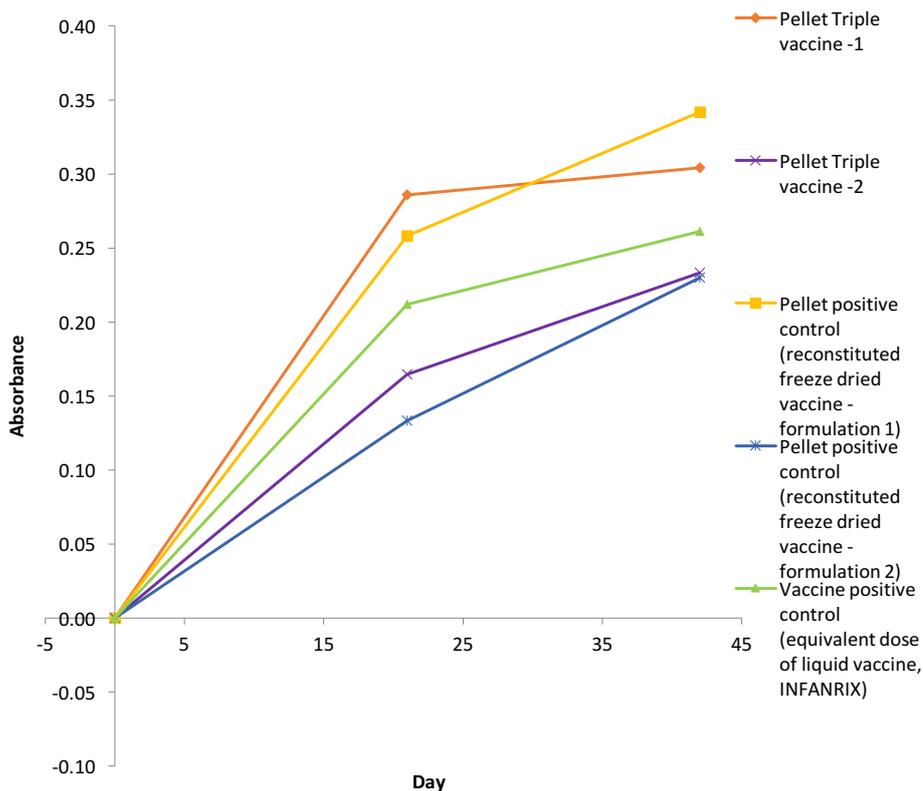


Figure 6: Pertussis toxoid immune response (DTaP Study).

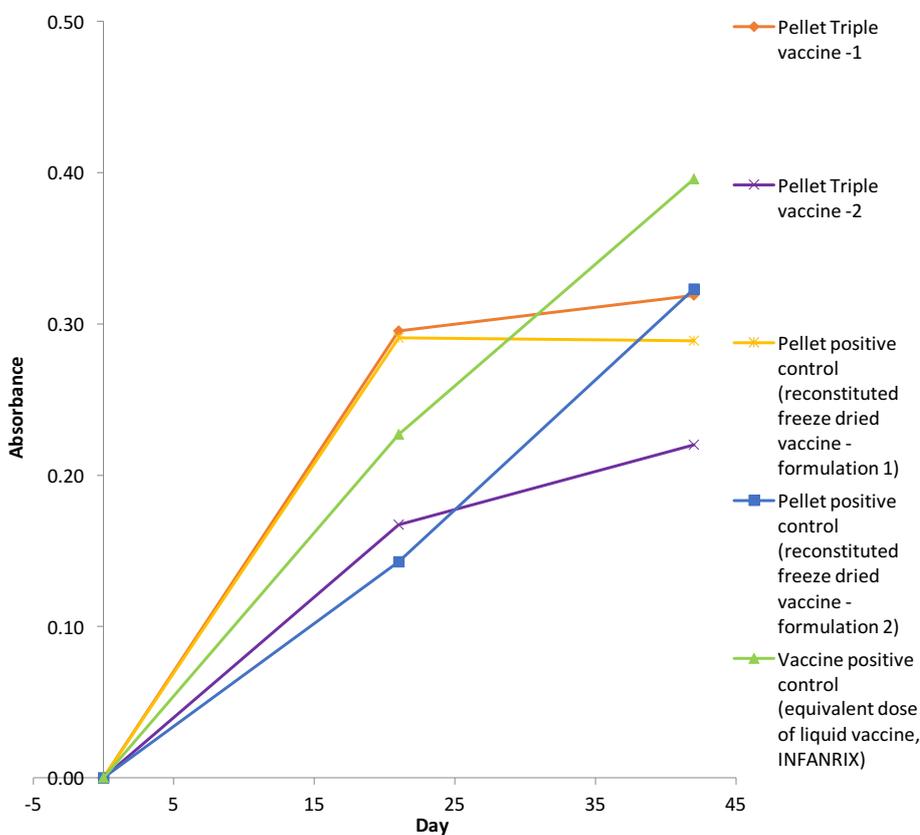


Figure 7: Pertussis immune response (filamentous haemagglutinin (FHA) vaccine arm) (DTaP Study).

pellets. However, the dose of triple vaccine was significantly lower (approximately 2% of a human dose compared with 25% and 6% for the high- and low-dose tetanus-only groups). The anti-tetanus response was very low at 21 days and no response was seen to diphtheria at this time point. However, a response to both was seen at 42 days after the boost dose. In contrast, the pertussis response was evident at 21 days with no significant increase at 42 days.

## DISCUSSION

The purpose of this study was to demonstrate the potential for solid-dose vaccine delivery using the Nemaura proprietary solid-dose injector technology. The data clearly show that solid-dose delivery of tetanus and DTaP vaccines resulted in immune responses. The tetanus study showed a dose-response effect with some indication of a possible dose-sparing effect when delivery was in the solid form. In addition, the DTaP study demonstrated that the freeze-drying process which was used to convert the vaccine to a solid form did not result in any observable loss in potency.

The study reported here is an encouraging step forwards in developing a vaccine delivery system which is straightforward to manufacture, a low-cost, disposable system, easy to use and avoids the problems associated with cold-chain delivery of vaccines and potentially other biologics.

Industrial processes for pellet manufacture are currently in progress and pellets of a significantly smaller size than those used for this preliminary study have also been developed by Nemaura. The technology is currently being evaluated for a number of molecules, and collaboration and business development enquiries should be sent to David Scott: [bd@nemaura.co.uk](mailto:bd@nemaura.co.uk).

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## THE CRITICALITY OF ADHESIVE SELECTION FOR OPTIMAL TRANSDERMAL DRUG DELIVERY SYSTEMS

In this piece, Megan Greth, Business Manager, ARx, LLC, and Gozde Karabiyik, PhD, Product Development Scientist, Adhesives Research, discuss why selecting the right adhesive for body-worn drug delivery systems – be they transdermal patches or wearable injection devices or pumps – is critical for a successful outcome.

The adhesive is an integral part of any active transdermal delivery device and passive short- and long-term wear transdermal patch. It is critical that an adhesive is selected or custom developed in consideration of the following key attributes when developing an effective and robust drug delivery system.

### SKIN-FRIENDLY ADHESIVES FOR ADVANCED DRUG DELIVERY SYSTEM PERFORMANCE

Drug delivery methods have expanded in scope and capability, which has created a need for new adhesive technologies to overcome skin bonding challenges. Development of new active transdermal

importance in the delivery of insulin and other biologics to subcutaneous tissue.

Skin adhesives are critical components for both transdermal patches and drug delivery device applications to ensure firm bonding on skin to deliver target therapeutic dose. Adhesive and skin bond must withstand moving and lifting due to physical activity, constant friction from clothing, moisture exposure and varying degrees of skin oil levels. In drug delivery device applications, such as patch pumps and infusion sets, further challenges arise from the weight of the device filled with drug and limited moisture vapour transmission of skin adhesive under the device. It is also important to note that a number of factors

“It is also important to note that a number of factors including age, race and patient health contribute to skin variations. Likewise, variations of skin surface energy and skin stretching at different body locations affect wear performance.”

drug delivery systems (TDDS) has enabled the delivery of larger compounds through the *stratum corneum*. Additionally, body-worn drug delivery devices have gained

including age, race and patient health contribute to skin variations. Likewise, variations of skin surface energy and skin stretching at different body locations affect



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Figure 1: Biocompatible, skin-friendly adhesive.



Figure 2: Application of a SoftWear® low-trauma adhesive transdermal patch.

wear performance. All of these factors must be considered by an adhesives expert in order to achieve a consistent delivery profile across a specified patient population.

#### ADHESIVE REQUIREMENTS: BIOCOMPATIBILITY & BREATHABILITY

Adhesive biocompatibility is a significant concern in skin adhesive applications. Presence of any residual monomers and leachable components, particularly acrylics and natural rubber-based adhesives, could potentially cause skin irritation and sensitisation. Skin adhesives should be formulated carefully to provide a biocompatible adhesive system to prevent

any adverse skin reaction (see Figure 1). In addition, skin breathability through the adhesive is essential to prevent maceration during wear.

In some applications, maintaining a certain hydration level at skin and adhesive interface is critical for enhancing drug flux. In this case, the skin becomes weak due to maceration and it can result in potential tearing and pain during device removal. Adhesive breathability depends on the moisture vapour transmission rate (MVTR) of the skin patch and body-worn device design as well as the adhesive construction. Breathability of a skin adhesive can be increased via substrate selection, lowering adhesive coat weight and zone or pattern coating.

“Adhesive breathability depends on the MVTR of the skin patch and body-worn device design as well as the adhesive construction. Breathability of a skin adhesive can be increased via substrate selection, lowering adhesive coat weight and zone or pattern coating.”

#### SKIN-FRIENDLY, AGGRESSIVE ADHESIVES FOR LONG-TERM WEAR

Several currently available transdermal patches are designed to be removed within 24 hours of application. However, new applications are designed for longer wear time extending wear duration up to multiple days for continued controlled release. Current seven-day, passive transdermal patches on the market are provided with an adhesive overlay to assist with bonding for the desired time period. In addition, several body-worn drug delivery devices are designed to adhere on the skin beyond seven days.

Adhesives Research has designed a tailorable, pharmaceutical-grade, acrylic-based adhesive technology that provides an aggressive long-term wear (LTW) adhesive platform to secure a drug delivery patch or device on skin for up to seven days. This adhesive platform ensures bonding of the tape to skin with minimal edge lift during the course of wear and removes from the skin cleanly without leaving any residue. This adhesive platform provides high MVTR for breathability and good wear properties with no edge residue or cold flow.

Aggressive adhesion on skin offers a secure bond to prevent lifting or moving of the patch. In spite of the aggressiveness of the LTW, it has a pain index of <2.5 on the Wong-Baker FACES® Pain Rating Scale and pain experienced upon removal of the tape is tolerable. Studies have also shown that removal of the adhesive tape does not cause disruption of stratum corneum. This adhesive formulation can be further tailored to customise the wear time and pain level depending on the wear duration and the delivery application.

## SOFTWEAR® LOW-TRAUMA ADHESIVES FOR SHORT-TERM WEAR

There is a growing need for low-trauma adhesives to provide reliable adhesion on different skin conditions and age groups with gentle removal from skin. Moreover, treatments for chronic conditions require repeated application (see Figure 2) and removal of a skin patch on specific skin site. Adhesives Research is addressing the growing need for gentle and repositionable skin adhesives through the development of low-trauma adhesive (LTA) technology

The adhesive is formulated to release from hair and the top layer of skin cleanly, with a pain index of <2.5 on the Wong-Baker FACES® Pain Rating Scale.

For comparison purposes, a standard skin-friendly adhesive has a pain index rating of 4–5 on this scale, based on Adhesives Research's studies. In addition, LTA formulations exhibit resistance to radiation sterilisation techniques. This is important in applications such as microneedles and abrasion, providing an advantageous alternative to standard adhesives available on the market.

approximately 35 years. However, the issue of cold flow still exists and has received heightened attention in recent years. As both time from date of manufacture and wear time increase, so does the ability for the adhesive matrix to flow outside of the patch backing layer and seep into the packaging foil or form a ring of residue on the skin. This phenomenon is not only aesthetically displeasing and inconvenient, but it can also impact the drug flux of the patch.

In recent years, the US FDA and various journals have discussed mechanisms to characterise cold flow. The FDA also references cold flow as a consideration in the Quality by Design section of its August 2011 guidance, "Residual Drug in Transdermal and Related Drug Delivery Systems". As with all Critical Quality Attributes, the minimising of cold flow has to be designed into the patch. Scientists must take careful consideration in selecting the appropriate adhesive chemistry, as well as the interaction with the active pharmaceutical ingredients and any other enhancers. Adhesives Research and ARx scientists have the advantage of over 35 years of foundational expertise in adhesive polymers and the selection thereof when formulating transdermal patches.

"In recent years, the US FDA and various journals have discussed mechanisms to characterise cold flow. The FDA also references cold flow as a consideration in the Quality by Design section of its August 2011 guidance, Residual Drug in Transdermal and Related Drug Delivery Systems."

for gentle removal. This customisable, pressure-sensitive adhesive (PSA) platform technology, known as SoftWear®, maintains intimate skin contact for up to three days with residue-free, gentle removal from skin.

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# US FDA ISSUES GUIDANCE ON HUMAN FACTORS STUDIES FOR COMBINATION PRODUCTS

This is the second in a series of articles covering quality system requirements for combination products and borderline products in the US and EU. In February 2016, the US FDA issued three guidance documents which focus on identifying, assessing and mitigating hazards related to how people use medical products that include a medical device. In this Article, Adam Shames, MBA, Chief Executive Officer, Core Human Factors, and Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting<sup>®</sup> and Head, Combination Product Training Institute<sup>®</sup>, summarise the FDA's recently released draft Guidance: "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development".

## USE-RELATED HAZARDS

Combination product users, such as patients, professional and lay caregivers, pharmacists and physicians have unique needs that vary from product to product, but all users need all products to be safe and effective. Human factors engineering (HFE) and usability engineering (UE) provide the necessary tools to identify, assess and mitigate use-related hazards. According to the US FDA, the "goal is to...eliminate or reduce to the extent possible" anything related to the user-device interface "that could cause harm or degrade medical treatment". In particular: "Drug development should take into account the user interface and factors that can reduce the risk [of] medication errors, i.e. features to enhance patient safety." Note that "the user interface includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, and instructions for use".

The HFE/UE "processes can [also] be beneficial for optimising user interfaces in other respects (e.g. maximising ease of use, efficiency, and user satisfaction)" but FDA is "primarily concerned that device-containing

medical products are safe and effective for the intended users, uses, and use environments", and the guidance is focused on that singular goal. Therefore, manufacturers interested in other uses of HFE/UE besides risk control should look elsewhere. Some recommended guidance documents for those other goals are ANSI/AAMI HE75<sup>1</sup> and ANSI/AAMI/IEC 62366-1.<sup>2</sup>

## FDA GUIDANCE & DRAFT GUIDANCE

On February 3rd, 2016 the FDA issued three guidance documents describing how they expect industry to address use-related hazards as part of their overall risk-management process. The first document came from the Center for Devices and Radiological Health (CDRH) and is the final version of a draft that was published back in 2011. It is titled: "*Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff*".<sup>3</sup> The second document also came from CDRH and is a draft titled: "*List of Highest Priority Devices for Human Factors Review*".<sup>4</sup> The third document came from the Office of



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Combination Products (OCP) and is also a draft, entitled: “*Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff*”.<sup>5</sup>

Together, these guidances provide insight into how the FDA views the risks associated with use-related hazards and their expectations for how manufacturers should follow HFE/UE processes during the development of combination products.

## HUMAN FACTORS & USABILITY ENGINEERING

The HFE/UE process can start at any time. However, “user interface design flaws identified during formative evaluation [i.e. early, information-gathering human factors studies] can be addressed more easily and less expensively than they could be later in the design process”. The process is started and scaled appropriately when it is done in relation to the potential for harm as a result of use-related hazards. A typical HFE/UE process includes three steps, which the FDA calls “essential”.

They are:

1. The identification of use-related hazards
2. The elimination or mitigation of those hazards (i.e. the control of the hazards)
3. Demonstration that the hazards have been successfully & sufficiently controlled.

Whilst each product should have a process tailored to its unique characteristics, successful HFE/UE processes conclude with the same statement that the product “has been found to be safe and effective for the intended users, uses, and use environments”.

## USE-RELATED HAZARDS UNIQUE TO DRUG DELIVERY SYSTEMS

Drug delivery device use typically exposes users, particularly those self-administering, to at least the following hazards: overdose, under-dose, missed dose, inadvertent needle-sticks (when a needle is involved) and transmission of blood-borne pathogen (when a needle or other sharp is involved). Therefore, users of combination products which are intended for drug delivery must be able to prepare properly and administer

the drug safely at the labelled/prescribed dose and assure correct disposal. Also, users must be able to distinguish the product from others of similar appearance such as when medication for other conditions and for “other family member or pets” is “stored in the same location”.

## USERS

Professional caregivers (such as nurses and physicians), lay caregivers (friends and family), and patients are all exposed to the use-related hazards associated with combination products. According to the FDA, a determination of user groups examines whether use-related hazards that may affect two or more people can be analysed, controlled and evaluated in the same manner. If there are “meaningful differences in capabilities or use responsibilities between user populations that could affect their interactions with the device (such as lay and professional users who might use the same device to perform different tasks or different types of professionals who might perform different tasks on the device)”, then there are different,



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unique user groups. Further, for combination products, users may be grouped as nurses, pharmacists, physicians, emergency medical technicians, home health care providers, lay caregivers and self-administering patients. In addition, since a user's experience may affect how they use a product, it may be necessary to include groups of users with and without "experience of similar-appearing products with different instructions for use or different hazards".

Training is only appropriate as a last resort to control a use-related hazard. If training is necessary to control a use-related hazard, FDA says: "It is important to determine what the training is likely to encompass and how it will be performed, who is responsible for conducting the training" and "whether there is an expectation that training will routinely and consistently occur, before the first use of the combination product".

"Together, these guidances provide insight into how the FDA views the risks associated with use-related hazards and their expectations for how manufacturers should follow HFE/UE processes during the development of combination products."

#### USING TRAINING TO CONTROL USE-RELATED HAZARDS

The following controls are in order of priority: 1) inherent safety by design; 2) protective measures; and 3) information for safety (including training). How FDA prioritises the use of these controls to mitigate design flaws is clear in the guidance and is consistent with established international standards such as ANSI/AAMI/ISO 14971.<sup>6</sup>

When training "is not expected to routinely or consistently occur", human factors testing "should evaluate the user interface in the absence of training". When training is included in human factors testing, the testing "should simulate the effect training decay may have on the users. e.g. simulate the training decay by separating the training and simulated use testing by several hours or days". The specific interval of decay should be justified in the study protocol and training materials.

#### HUMAN FACTORS STUDIES & CLINICAL STUDIES

According to the draft guidance, the human factors validation study (which is the study intended to "demonstrate that the final finished combination product user interface would maximise the likelihood that the product will be safely and effectively used by intended users, for the intended uses in the intended use environments") should ideally occur before conducting major clinical studies (i.e. studies intended to "provide the primary support for the safety and effectiveness of a product for a proposed indication").

If the final finished combination product will be used in major clinical studies, the human factors validation should be conducted on the final finished combination product prior to initiating major clinical studies. However, FDA acknowledges that the "sequencing of the human factors study prior to the clinical study may be less critical to inform our understanding of the product's safety and efficacy".

Further, "in some cases it may be appropriate to conduct your human factors studies in parallel to your major clinical studies or after your clinical studies to address modifications to your product".

While these studies can be conducted sequentially or in parallel, it is nearly impossible to conduct one study to support both objectives. This is due to the fundamental nature of most of these studies – that they are controlled studies in which independent variables are controlled and dependent variables are not controlled. In clinical studies, use of the combination product is typically one of the independent variables that needs to be controlled and this is the exact opposite in human factors studies in which use of the combination products is the dependent variable and is therefore not controlled. Use in a human factors study should not be controlled because use of the combination product is specifically what is intended to be evaluated.

#### SIMULATED VS ACTUAL USE

Most combination products should be evaluated in a simulated use study but there are some instances in which simulated use is insufficient to assess all aspects of safety and effectiveness. OCP proposes that there are two types of human factors validation studies: 1) simulated use, and 2) actual use. They further divide actual use studies

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Adam Shames is a recognised human factors expert and consultant and is the Founder and Chief Executive Officer of Core Human Factors, Inc, a leader in human factors and usability engineering consulting services with over 12 full-time employees. Adam holds an MBA in international business and a BS in human factors engineering and psychology. He received the De-Florez Prize in Human Engineering and holds a Certificate in Applied Ergonomics Training from the United States Army Center for Health Promotion and Preventive Medicine. Adam has over 15 years of human factors research experience and has served as the Principal Investigator on hundreds of IRB reviewed usability studies involving thousands of participants in cities around the world.

Michael Gross is the Principal Consultant of Chimera Consulting®, specialising in quality assurance, regulatory affairs and technical development of drugs, biologics, medical devices and combination products. He also heads the Combination Product Training Institute®, which provides professional training programs on combination product topics. Michael holds a PhD in Organic Chemistry and conducted post-doctoral research in biochemistry at the National Institutes of Health. He is a former FDA reviewer and inspector. Michael worked for 30 years in senior quality, compliance and regulatory affairs roles for a number of large and small pharmaceutical and medical device companies. Today, he provides an influential industrial perspective on the regulation of combination products and is a frequent speaker on combination products topics and has published numerous articles in regulatory and scientific publications.

into two subcategories: 2a) actual use in a simulated environment, and 2b) actual use in a real environment.

When simulated, the simulation should be sufficiently realistic so that the results of the study are representative of aspects of actual use of the product once introduced to the market. OCP states that “there are rare circumstances when it is difficult to simulate the conditions or use, physical characteristics of the product, or environment of use”, and it is therefore necessary to conduct an actual use study.

## LABELS & LABELLING

“In situations where the understanding of information provided in a combination product’s labels or labelling is a critical task to using a product safely and effectively, a study to assess the user’s understanding of such information (Knowledge Task study) is appropriate,” says FDA. Knowledge assessments focus on the understanding and interpretation of user interface information that will be applied in making use-related decisions. They differ from other types of human factors studies where critical task performance is assessed by observation.

Some of the critical tasks that may be evaluated in a knowledge assessment are: identification of defective/expired product, awareness/understanding of pertinent safety information in the instructions for use, recognition of clinical signs identified in the instructions for use that prompt medical attention and understanding labelling diagrams.

## SUBMITTING HUMAN FACTORS INFORMATION TO FDA

A use-related risk analysis “should [always] be submitted in an investigation application”, since a “combination product’s specific use-related risk analysis generally informs the Agency’s expectations” for whether additional human factors data should also be submitted. In general, additional human factors data should be submitted to the FDA as part of the application whenever there is potential for serious harm resulting from use error or whenever the FDA specifically requests it either through device specific guidance or while in consultation with an applicant. The FDA encourages applicants to contact them to discuss specific product proposals.

However, regardless of whether additional human factors data must be

submitted as part of the application, FDA expects that all applicants are compliant with 21 CFR 820.30 – Design Controls, which mandates the conduct and documentation of human factors activities throughout the design and development process.

The “FDA encourages applicants to submit the following human factors information for feedback before commencing the HF Validation study:

1. Use-related risk analysis and any updated risk analysis of design changes
2. A summary of human factors formative study results and analysis
3. A summary of changes made to the product user interface after the formative studies, including how the results from those studies were used to update the user interface and use-related risk analysis
4. The draft human factors validation study protocol
5. Intend-to-market labels and labelling (including instructions for use if any are proposed) that will be tested in the human factors validation study.

The FDA states that it “intends to provide preliminary comments on the user interface labels and labelling. However, final labelling is determined after review of the entire marketing application that includes information beyond that in the human factors validation study”. Depending on the outcome of its review, final approved labelling may differ from what is tested in the human factors validation study. Therefore, “an additional human factors validation study may be needed to ensure that the labelling changes minimise the use-related risks without creating additional hazards”.

## CONCLUSION

HFE/UE is a time-proven method for reducing use-related hazards. If products are not developed with awareness and implementation of HFE/UE controls, end-users will be more likely to injure themselves, or fail to receive needed medical treatment. This is why the FDA, which is responsible for regulating safety and effectiveness of drugs, biologics and medical devices, including combination products, has issued these new guidances to explain its current thinking on what actions are necessary during the development and post-market approval management of new products.

Please visit the Chimera Consulting® website ([www.ChimeraConsultingNA.com](http://www.ChimeraConsultingNA.com)) for additional analysis of the draft guidance.

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