

# Transdermal Delivery Frequently Asked Questions

## Regulatory Issues

Q) What is the difference between the various Transdermal delivery devices available on the US market?

A) In the US as a rule, regardless of individual technical characteristics and performances, when they talk about Transdermal Delivery they mean medical devices. Medical devices must have FDA clearance (or 510K number) to be able to be sold on the market.

Q) I am considering a new Transdermal Delivery machine. How do know it's a medical device?

A) Whoever is talking about Transdermal delivery must be able to show you and FDA clearance or 510K Number. In the US transdermal delivery means a medical device that requires FDA clearance.

Q) If the new product does not have FDA clearance what kind of machine am I dealing with?

A) All manufacturers of Transdermal delivery devices must have FDA clearance. If a manufacturer does not have that, the machine in question might be a micro-current device indicated for cosmetic and not medical applications.

Q) What if I want to use it anyway in-spite of the missing FDA approval?

A) In the US if a doctor wants to use this kind of machine he/she may do it.... but of course he/she assumes all responsibility for using a non medical (FDA) cleared machine in a medical environment.

Q) What does it means to have a FDA cleared machine vs. a non FDA cleared one?

A) FDA clearance is extremely important, especially in terms of liability, guarantee of efficacy and assurance of safety for both patients and doctors.

Q) My patients do not want needles. Is Dermoelectroporation® technology of any help with this?  
As the FDA Clearance statement says *“The Transderm® Ionto is a powered drug delivery system that is indicated for the local administration of ionic drug solutions into the body for medical purposes and can be used as an alternative to injections”*.

Q) For what kind of applications can I use the Transderm® Ionto System?  
US doctors using Transderm® Ionto System are successfully dealing with various applications such as collagen and hyaluronic acid transdermal delivery treatments, pre-laser treatments (anesthetic) for both hair removal and resurfacing. Some others are using Ultrapeel® Transderm® Ionto System with cancer drugs or steroid delivery. Some others are using Ultrapeel® Transderm® Ionto System for mesotherapy procedures etc...

Q) I'm a physician. Why should I consider Transderm® Ionto System?  
Transderm® Ionto System not only provides a non-invasive alternative to injections that may help in minimizing skin trauma, pain associated with needles and allow clients scared by syringes to have the huge benefit of minimizing concern over possible infectious disease hazards, but also allow users to deliver macromolecules (15Kdalton on ) in little time. This was not possible with other Ionophoresis systems.

Q) I'm a Physical Therapist. Why should I consider Transderm® Ionto System?  
Transderm® Ionto System provides an alternative to injections and a cost effective solution to improve patients' conditions within a therapy program. Caution - Ultrapeel® Transderm® Ionto System treatments must be prescribed by a physician to be used for specific therapies.

Q) My interest is in something that is limited to physicians rather than a product that every "doctor wannabe" can purchase.  
Transderm® Ionto System is for medical purposes only. As the FDA Clearance statement says: The Transderm® Ionto is a powered drug delivery system that is indicated for the local administration of ionic drug solutions into the body for medical purposes and can be used as an alternative to injections. It may only be used by doctors.

Q) Does Mattioli Engineering Corporation supply ionic drug solutions?  
No. Mattioli Engineering Corp. does not supply nor package ionic drug solutions with the machines.  
Other companies sell appropriate ionic drug solutions.

Q) I'm a Medical Doctor. Can I use the ionic drug solution I wish?  
On your own indication you may use the ionic drug solution you choose.

Q) What kind of Lidocaine do the doctors use for pre-laser treatment?  
Some are using a brand of 2% Lidocaine HCl 1:100.000 epinephrine;

Q) I would like to know specifically how your product compares with the others products being used in other countries (for example Canada).  
Let's say that on the market there are two type of devices:

1) Micro-current devices (less than 1 mA output) to be used in Cosmetic application that do not require FDA clearance. These devices are not for medical use and cannot be used, following FDA and US Rules, in medical applications.

2) Medical devices (more than 1 mA output). They must be FDA cleared and can be used only for medical application by a physician.

At the present time Transderm® Ionto System is the latest FDA cleared machine for Transdermal Delivery using new pulsed technology instead of DC current; it is recognized as a medical device for transdermal delivery of ionic drug solutions into the body. US rules enable the use for cosmetic purposes only micro-current devices that are well known to be ineffective.

So the Canadian device, for instance, must have US FDA clearance otherwise they are micro current cosmetic devices AND if the Canadians are marketing the device as a Medical Device without any FDA clearance they are illegally marketing according to US regulations. To be FDA cleared is important, especially to avoid liability, assure efficacy of performance, and safety for doctor and patients.

Q) How large a molecular size can you get in via Ionthophoresis? Growth factors? Collagen? Maybe you have a list of materials that are known to be transported effectively.

A) Macromolecules (more than 15Kdalton in size to thousand of Kdalton). Doctors deliver Hyaluronic acid, Collagen, Heparin, Elastine, precursors, amino acids, Vitamins...etc....

Q) Does Transderm® Ionto System require a charged ionic material? How about materials that are not ionic? Do you use a carrier to deliver products, or do you provide them right at the tip without any carrier solution.

Transderm® Ionto System does not need any charged compound nor carrier to do the job. Non ionic drug solutions are not indicated to be used with Transderm® Ionto System. The system itself delivers the ionic drug solution (water based) from the probe to the patient in a timely manner through a Precision Liquid dispenser (PLD).

Q) Can I deliver Gels or cosmetic creams with Transderm® Ionto System ?

Non ionic drug solutions are not indicated to be used with Transderm® Ionto System. For instance Creams and Gels due to their own enhancers and carriers that can penetrate too deep and cause irritation of any sort to the patient are not indicated.

Q) Does Ultrapeel® Microdermabrasion improve transport? Do I need to spend lot of time for that?

Ultrapeel® Microdermabrasion promotes transdermal delivery of course but you do not need to do a complete peeling treatment. Only a few seconds peeling on the area to be treated need be performed - just to peel away the stratum corneum and increase porosity.

Q) For instance, if you are using it to provide topical anaesthesia for hair removal for a man's back, wouldn't this take more time than applying topical anaesthetic cream?

Here it depends on what your goal is. Do you want to reduce the time of treatment for your patient (including patient's waiting with the cream), so that your patient becomes your first marketing tool?

Q) Is Transderm® Ionto System contraindicated for patients with a cardiac pacemaker or defibrillator?

According to FDA guidelines, the use of any electrotherapy device with a demand type pacemaker or defibrillator is contraindicated.

Q) Can Transderm® Ionto System safely be used with a pregnant patient?

The safety of any Ionthophoresis with this patient population has not been established in the

literature to date. So the use in these particular conditions is not encouraged.

Q) Are there any safety concerns about using a Transderm® Ionto System device around machinery or with other implantable medical devices?

Some machinery or implantable medical devices may interfere with the operation of Transderm® Ionto System device. Examples include equipment that generates high frequency or high energy electromagnetic radiation, patient monitoring equipment, and external defibrillators.

Please refer to Transderm® Ionto System Operating for a complete list of contraindications, warnings and precautions.

Q) Might Transderm® Ionto System cause irritations or allergies ?

From experience to date, Transderm® Ionto System as a methodology does not cause any allergy or irritation. What may cause allergies or irritations are the ionic drug solutions delivered into the skin that are not either part of the machine itself nor belonging to the machine.

The only limitation is the eye area.

Mattioli Engineering strongly recommends not to go over the eye area in order to avoid possible problems with the retina (not exactly known at this time).

Q) Might Transderm® Ionto System cause red areas on the skin?

During normal use, little areas of redness may appear and disappear in a few minutes. Mattioli Engineering suggests not to exert pressure while using the machine to avoid redness on the face particularly.

Q) Can I use an Transderm® Ionto System device as a device for pain control?

Doctors are using Transderm® Ionto System for pain management applications with no problems reported to Mattioli Engineering.

Q) Is there any particular Transderm® Ionto System headprobe placement to be more effective on patients?

None in particular. Small circular movements without strong pressure allows users to get to the best treatment in minimal time.

Q) How long does a treatment last? And how frequently do I have to repeat the session?

It depends on the treatment. There is no a general rule. Everything is physician dependent.

Q) What can I do if the red LED lights up on the Transderm® Ionto System head probe?

Red LED means that the user is not making sufficient contact with the patient's skin. Just reposition to ensure good contact on the skin.

Q) Right in the middle of the treatment I need to disconnect the probe from the patient. What can I do?

First, decrease the current to "0" to prevent patient feeling pulses in spite of the selected vibration. Then stop the vibration and disconnect the Transderm® Ionto System head probe from the skin.

Q) Do you have any deliver cap electrodes that might contain latex?

No. All Transderm® Ionto System drug delivery cap electrodes, accessories and equipment products are latex free.

Q) Are drug delivery cap electrodes reusable?

No, they are disposable and must be replaced between each treatment.

Q) What can I do if the electrodes aren't sticking well to Transderm® Ionto System drug delivery cap?

If the electrodes are not sticking properly, they have to be replaced with another one.

Q) Can I use rubbing alcohol to clean the head probe ?

No. Rubbing alcohol should not be used to clean either the electrodes or skin. It can adversely affect electrode life and can be very drying and irritating to the skin.

Q) What should be done if the treatment area is extremely hairy, i.e. legs, arms?

Excess body hair should be trimmed, not shaved prior to electrode use, as shaving can cause skin irritation.

Q) How do I determine the best dosage and total number of treatments for a patient?

The dosage and number of treatments depends on the desired outcomes and response of each patient considering the ionic drug solution to use. The total number of treatments varies depending on the patient's response, the medication being administered, and the severity of the condition.

Q) Can it be used for Botox injections

There are clinical evaluations in progress showing very promising results but there are no clinical data available on the topic.

Q) Disposable cost per treatment

The disposable cost per Treatment is approximately \$3 - 6 (maximum retail price on microdermabrasion) + \$8.60 (maximum retail price on a single drug dispensing cap)

Q) Overall experience with this equipment

Around 4 years worldwide

Q) What technology does Transderm® Ionto System use?

Transderm® Ionto System uses Dermo-electroporation® Technology.

This features pulsed Iontophoresis (Low currents from 1 to 5 mA as the medical devices rules require) with “electroporation-like” pulses waveform shape (and only the shape no other parameters)

Q) So Transderm® Ionto System is an Iontophoresis machine equal to others already on the market right?

No . Transderm® Ionto System is the newest alternative to traditional iontophoresis systems due to its specific pulses waveform and delivery methods. As a matter of fact there is no separate return electrode.

Q) What is Iontophoresis?

**Ionto = Ions Phoresis = Transport .**

**Iontophoresis** means “ions delivery” into the skin.

**Traditional Iontophoresis**, is a process to enhance the penetration of ionized substances into or through a tissue by the application of an appropriate electrical potential (*Singh et al., 2001*).

Iontophoresis is an active (electrically driven) method of delivering drugs and can be a more effective option than passive drug delivery through a transdermal skin patch.

Traditional Iontophoresis has always been fascinating technology manufacturing companies along with patients that “**do not like needles at all**”. Traditional Iontophoresis is based on the fact that “many compounds are composed of positively and negatively charged ions. When these compounds are placed in an appropriate solution, they dissociate into their polar components and assume a + or - charge. While in a charged state, each ion can be influenced by an electrical field created within the solution. + charged ions (cations) will be attracted to the – pole (cathode) and repelled from the + pole (anode) and vice versa. The electro repulsion of like charges is the driving force for Iontophoresis. - *Muslimah Rashed, SPT-Wayne State University Graduate Seminar Nov. 6, 2002.*

This “electrotherapeutic technique” uses a **galvanic current** to "push" a drug (active substance) into the patient's skin. The active substance (negatively or positively charged) is applied all over the electrode that has the same polarity (cathode or anode). The ions will migrate into the skin as a result of the repulsion of the similar electrical charges.

However, there are some side effects associated with this technique:

a) **electrolysis** reaction at the site of the electrodes: This causes a degradation of the molecule being inserted. Transderm® Ionto System, instead, does not have any electrolysis thanks to the particular pulses we deliver and no return electrode needs to be located elsewhere but inside the active electrode area.

Furthermore, the substances are mainly absorbed at the intracellular level, with poor delivery of macromolecules.

Since the galvanic current increases the skin's temperature and may produce burning feeling, it is generally accepted that traditional Iontophoresis may be uncomfortable for the patient.

b) **Change of ionic drug solution PH:** This may potentially irritate the skin and cause inflammations more frequently located on the negative electrode and particularly for longer treatments sessions. Transderm® Ionto System does not change the ionic drug solution PH instead due to the fact that it delivers both positive and negative ions into the skin so we do not modify the ionic drug solution through our particular pulses delivered.

c) **Small sized molecules delivery only:** DC current devices cannot deliver large sized molecules because of their way of transdermal delivery. Doctors in the US are using Transderm® Ionto System are able to deliver such ionic solutions such as Hyaluronic acid or steroids and another one some anti-cancer drugs (That are definitely very big molecules!).

Q) Is Dermoelectroporation equal to Electroporation?

**Not at all.**

Transderm® Ionto System uses only the waveform SHAPE of electroporation techniques and not current peak values, pulses durations and other electrical parameters that might be affecting the patients in anyway. Please see below about the difference between Dermoelectroporation® technology and Electroporation.

**Dermoelectroporation®**

Dermoelectroporation® technology is a new, patented proprietary technology from Mattioli Engineering Research Labs. It is a non-invasive method of delivering drugs into the body. Dermoelectroporation® causes the skin to create “channels” to allow ionic drug solutions to penetrate due to controlled “electroporation-like” continuous reversed polarity electrical pulses increasing the skin’s permeability and allowing transdermal delivery of drugs as occurs in classical Iontophoresis, even if the average current value is zero. This pulsed Iontophoresis with safe, current-limited, pulsed “Electroporation-like” waveforms allow both micro-molecules and macro-molecules to be delivered into the body without modification of the ionic drug solutions pH and avoiding the electrolytic effect at the electrodes and electrolysis of the ionic solution itself. Because there is no change in the pH of the skin, it is possible to perform microdermabrasion immediately before Dermoelectroporation®

Pre-treatment microdermabrasion of this sort increases the transdermal delivery rate and ensures repeatability as a result of the standardization of the thickness and permeability of the stratum corneum. This exciting new combination opens up new fields and uses for Mattioli Engineering’s existing microdermabrasion technology. Also the vibration feature significantly decreases the patient’s perception of electrical pulses.

Dermoelectroporation® Technology has no effect on the ionic drug solution being administered.

**Electroporation instead,** is a non-invasive method of delivering drugs into the body. When a High-level electrical current is applied to a drug solution, Electroporation drives the drug ions through the skin breaking the stratum corneum through high peak current.

In addition to this, the "Electroporation" methodology is not FDA approved in the US due to its high risk of side effects and skin damage. In the US they use Electroporation only in selected worse Cancer cases patients but it is not FDA cleared for any applications due to its high currents and side effects.

Q) I believe almost all of the technology comes from Italy right?.

**Right.** Transderm® Ionto System is manufactured by Mattioli Engineering Italia SPA of Florence Italy leading the Microdermabrasion market for more than 13 years.

## Ultrapeel Transderm Ionto System Frequently Asked Questions

Q)What is Transderm® Ionto?

A) The Transderm® Ionto is a powered drug delivery system that is indicated for the local administration of ionic drug solutions into the body for medical purposes and can be used as an alternative to injections. In other words, it must be used by a doctor and only with approved substances.

Q) How does Transderm® Ionto System work?

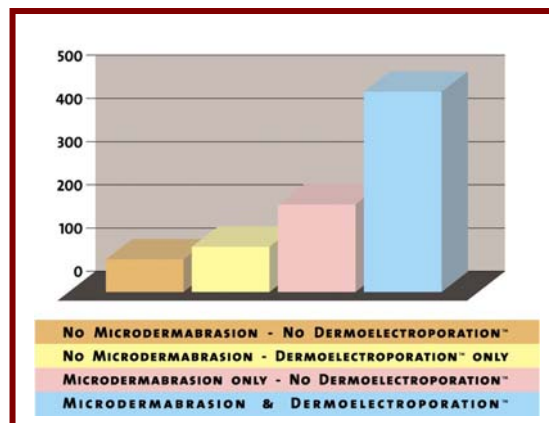
Mattioli Engineering's **Transderm® Ionto system** allows for the transdermal delivery of ionic drug solutions into the body. Transdermal delivery enables active principles to enter the dermis with no need of injections or syringes. Ultrapeel® Transderm® Ionto System combines traditional microdermabrasion with Dermoelectroporation®, and is designed to provide the benefits of transdermal drug-delivery treatments without the limiting side effects of other traditional techniques.

**Transderm® Ionto system** uses microdermabrasion - To exfoliate the stratum corneum and to ensure reproducibility - and **Dermoelectroporation®** Technology - allows the principle to enter the dermis by means of low energy, electrical pulses- to deliver Ionic drug solution into the body.

**Dermoelectroporation®** Technology when combined with **microdermabrasion**, boosts the transdermal delivery rate to get a higher flow than normally obtained from a Topical application (5 times the topical Application – see Fig.1)

FIG.1 – Delivery rate graph:

Using both microdermabrasion and Dermoelectroporation Technology it is possible to get to a delivery rate 5 times greater than a topical application.



Q)What is Transderm® Ionto System indicated for?

As the FDA Clearance statement says: The Transderm® Ionto is a powered drug delivery system that is indicated for the local administration of ionic drug solutions into the body for medical purposes and can be used as an alternative to injections.

**Q)What is Dermoelectroporation®?**

Dermoelectroporation® technology is a new, patented proprietary technology from Mattioli Engineering Research Labs. It is a non-invasive method of delivering drugs into the body.

Dermoelectroporation® causes the skin to create “channels” to allow ionic drug solutions to penetrate due to controlled “electroporation-like” continuous reversed polarity electrical pulses increasing the skin permeability and allowing transdermal delivery of drugs as occurs in classical Iontophoresis, even if the average current value is zero. This pulsed Iontophoresis with safe, current-limited, pulsed “Electroporation-like” waveforms allows both micro-molecules and macro-molecules to be delivered into the body without modification of the ionic drug solutions pH and avoiding electrolytic effect at the electrodes and electrolysis of the ionic solution itself.

Because there is no change in the pH of the skin, it is possible to perform microdermabrasion immediately before Dermoelectroporation®

Pre-treatment microdermabrasion of this sort promotes the transdermal delivery rate and ensures repeatability as a result of the standardization of the thickness and permeability of the stratum corneum. This exciting new combination opens up new fields and uses for Mattioli Engineering’s existing microdermabrasion technology. Also the vibration feature significantly decreases the patient’s perception of electrical pulses.

Dermoelectroporation® Technology has no effect on the ionic drug solution being inserted.

**Q) How will the Transderm® Ionto benefit my practice?**

Dermoelectroporation® technology offers several great advantages over classical Iontophoresis equipment because it can transdermally deliver macromolecules, where classical Iontophoresis devices cannot. Furthermore, because Dermoelectroporation® can be used following microdermabrasion, the combination allows for ionic drug solutions to be quickly delivered through the dermis. (This combination is not possible with Iontophoresis due to the alterations in the pH of the skin and the subsequent increase risk of side effects.)

**Q )How about the advantages I may get using Transderm® Ionto System Vs other systems?**

**It is FDA Cleared for Medical Applications.**

*As the FDA Clearance statement says: The Transderm® Ionto is a powered drug delivery system that is indicated for the local administration of ionic drug solutions into the body for medical purposes and can be used as **an alternative to injections**.*

**Capability of Transdermal Delivery of ionic solution of drugs.**

*(Transderm® Ionto System is a pulsed Iontophoresis machine able to deliver small sized molecules in half time of traditional Iontophoresis machines. – same dosage sample)*

**Capability of Transdermal Delivery for the first time ever of ionic solutions of macromolecules.**

*(Never happened before. Transderm® Ionto System allows users to have in only one device a machine capable of delivering very large molecules without utilizing high peak currents and causing discomfort to the patient. Large molecules in a very comfortable way.)*

**No electrolysis of ionic drug solutions.**

*(This ensures that the substance penetrates as a whole. Traditional DC current technology cause ion separation.)*

**No variation in the ionic drug solution pH.**

*(This ensures no irritation even for long lasting treatments.)*

**Promotes transdermal delivery rate by means of microdermabrasion and pulses delivery.**

*(In this way we can go down 5 times faster than a topical application with no risk)*

**Reproducibility of dose delivered due to preliminary microdermabrasion.**

*(Due to microdermabrasion we can reproduce the dosage delivered in any situation)*

**Vibration feature to minimize the electrical pulses perception on patients.**

*(Transderm® Ionto System will be one of the greatest experiences your clients will have. No electrical pulses sensation due to the vibration that reduces significantly the sensation on the patient)*

**Non-Invasive action. No trauma from injections.**

*(Transderm® Ionto System is the Alternative to injections. So what's best? No needles, no pain, no trauma but a very comfortable and effective experience for patients scared by needles.)*

**Q) How deep can we deliver ionic drug solutions?**

Transderm® Ionto System is recognized to be able to deliver transdermally until muscle membranes.

**Q) Does Ultrapeel® Transderm® Ionto System need any carrier product to be effective?**

A) No, Transderm® Ionto System does not need any carrier to be effective. Due to the Dermoelectroporation technology we just need the ionic drug solution to deliver and that's it.

**Q) Does Ultrapeel® Transderm® Ionto System need any charged ionic drug solution to be effective?**

A) No, Transderm® Ionto System does not need any charged ionic drug solution to work. Due to the Dermoelectroporation technology we just need the ionic drug solution to deliver and that's it.

**Q)What Transderm® Ionto System is not**

***The Transderm® Ionto is not:***

- *An ultrasound device*
- *An aesthetic-purpose unit*
- *A cosmetic device*
- *A multi-device unit*
- *A massager*
- *A microcurrent device*

**Q)What substances or active principles can be used with the Transderm® Ionto System?**

Iontophoresis devices are cleared for all approved Iontophoresis drugs. Therefore, you may choose the ionic drug solution that is best suited for the specific application based on the existing medical literature.

**Q) For what kind of applications can I use Transderm® Ionto System?**

US doctors using Transderm® Ionto System are successfully dealing with various applications such as Collagen and Hyaluronic acid transdermal delivery treatments, pre-laser treatments (anesthetic) for both hair removal and resurfacing; some others are using Transderm® Ionto System with cancer drugs or steroids delivery ; some others are using Transderm® Ionto System for mesotherapy procedures etc...

**Q) Is the Transderm® Ionto System costly?**

Ask to your Distributor for quotations