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PHARMACEUTICAL

# Advancements in Intradermal Delivery: From Historic Techniques to Modern Innovations



# Abstract

Intradermal delivery has long been a critical method in medical and pharmaceutical fields, offering unique advantages for diagnosis, vaccination and therapeutic applications. This white paper explores the evolution of intradermal delivery methods, comparing historic methods of delivery such as the Mantoux technique with modern innovations such as the Terumo Immucise™ Intradermal Injection System.

Additionally, it discusses the expanding applications of intradermal delivery, including its potential for targeted lymph node delivery.

# Intradermal Delivery

Intradermal delivery involves administering substances directly into the dermis, the skin layer rich in immune cells. This method has been utilized for over a century, primarily for vaccinations and diagnostic tests. The dermis is extremely rich in various resident and recruited types of dendritic cells, which play a critical role in the human immune response by capturing antigens and presenting them to T cells. Intradermal (ID) administration of vaccines can potentially result in quantitatively or qualitatively superior immune responses compared to intramuscular (IM) or subcutaneous (SC) injection.<sup>1</sup>

Terumo Corporation recently announced the commercial launch of its Immucise™ Intradermal Injection System, designed to deliver vaccines and other approved drugs to the dermal layer of the skin. This is a vertical puncture type intradermal injection device that is applied perpendicular to the surface of the skin in the deltoid region.<sup>2</sup>

This paper aims to compare historic intradermal delivery methods with modern advancements and explore new applications, particularly in the context of targeted lymph node delivery.

# Historic Intradermal Delivery Methods

Intradermal delivery has a rich history, with several techniques and devices developed over the years, with the aim to improve the efficacy and accuracy of substance administration into the dermis.

The Mantoux technique, developed in the early twentieth century, is one of the most well-known methods for intradermal delivery. In the U.S., the Mantoux tuberculin skin test has been the standard method for detecting latent tuberculosis (TB) infection since the 1930s. To perform the ID injection, the needle is inserted slowly with the bevel against the patient’s skin, and at a 5- to 15-degree angle. The needle bevel is advanced through the epidermis to a depth of approximately 3 mm. The injection will produce inadequate results if the needle angle is too deep or too shallow. The tuberculin solution is then slowly injected and a tense, pale wheal of 6 to 10 mm in diameter appears over the needle bevel.<sup>5</sup>

The Mantoux technique has several advantages, demonstrated by a legacy of decades of clinical and epidemiological research in testing for TB in the U.S., where the technique has shown its simplicity (e.g., no laboratory equipment needed), and low cost.<sup>7</sup> However, the accuracy and the consistency of an ID administration by the Mantoux technique with a standard syringe and needle mostly depend on the performance of the practitioner.<sup>4</sup>

Advancements in technology have led to the development of modern devices aiming to enhance the precision, ease of use, and patient comfort in intradermal delivery.

# The Immucise™ Intradermal Injection System: Considerations for Practitioners and Patients

Terumo’s Immucise™ Intradermal Injection System has been designed to deliver vaccines and other approved drugs to the dermal layer of the skin. The system is designed to be simple enough to handle easily and is expected to reduce risks of damaging tissues, such as blood vessels and peripheral nerves, due to its thin and short needle.<sup>4</sup> In use, the system has advantages over traditional ID delivery methods.

First, the device is applied perpendicular to the surface of the skin in the deltoid region, supporting precise and consistent delivery.<sup>2</sup> In a US FDA guidance-based human factors engineering study on the Immucise™ Intradermal Injection System, (*“Immucise™ Intradermal Injection System Human Factors and Usability Engineering Study Report”*), conducted by Terumo, a group of healthcare professionals (55 participants including physicians, primary care nurses, and pharmacists) were able to complete an injection using the Immucise™ Intradermal Injection System without use error on critical task, and without receiving any prior instructions on the system. Furthermore, delivery was conducted without causing serious harm through accidental needle stick injury.<sup>3</sup> This differs from the Mantoux technique, where the accuracy and the consistency of an ID administration, by using a standard syringe and needle, mostly depends on the performance of the practitioner.<sup>4</sup>



The needle of Immucise™ Intradermal Injection System is sized (i.e., outer diameter, bevel and length) so that the needle tip is retained in the dermal layer of the skin. The needle, has an outside diameter of 0.2 mm (33G) and is 1.15 mm long, and has a bevel length of 0.6 mm.<sup>2</sup>

The Immucise Intradermal Injection System is FDA cleared and indicated for intradermal injections of FDA approved drugs. The system is to be used in the deltoid region for infants aged two months (excluding low birth weight and/or preterm birth) to adults.

The device is also CE marked and is intended to be used for the intradermal injection of approved formulations.

# Intradermal Vaccination

Driven by its innate ability to generate an enhanced immune response, dose sparing, and the expansion of its use to deliver a wider variety of vaccines and other therapeutics, intradermal delivery is increasingly popular. <sup>1</sup>

## Enhanced Immune Response

The dermis is extremely rich in various resident and recruited types of dendritic cells, which play a critical role in the human immune response by capturing antigens and presenting them to T cells. Intradermal administration of vaccines can potentially result in quantitatively or qualitatively superior immune responses compared to intramuscular or subcutaneous injection. <sup>1</sup>

## Dose Sparing

Because of the ID route’s ability to enhance immune responses, smaller doses of a vaccine can achieve the same immunogenic effect achieved through means of delivery. Numerous studies have demonstrated these dose-sparing effects for ID delivery of several vaccines, such as seasonal influenza and rabies. This is particularly valuable during vaccine shortages or in low-resource settings and allow for dose-sparing, making vaccines more accessible and cost-effective. <sup>1</sup>

## Expansion of Use

Intradermal delivery is already used for certain vaccines, such as the rabies and BCG (tuberculosis) vaccines. (1) This established use provides a foundation for expanding ID delivery to other vaccines, leveraging its potential for broader immunization efforts.

# Clinical Trials

In a paper titled, “Immunogenicity and safety of the new intradermal influenza vaccine in adults and elderly: A randomized phase 1/2 clinical trial,” Ryo Arakane, et. al., (4) investigated the immunogenicity and safety of single, and two-dose vaccination and three different dose strengths (6, 9, and 15 g HA per dose) of the influenza vaccine using the Immucise™ Intradermal Injection System and comparing it with the standard SC vaccine (15 g HA per dose).

The Immucise™ Intradermal Injection System, showed a similar safety profile to that of SC administration, and the seroprotection rate for strain B by ID administration of 15 µg of influenza vaccine was 69.4%, whereas by SC administration the rate was 48.0%. 15 µg ID administration of influenza vaccine with Immucise™ Intradermal Injection System showed a higher seroprotection rate compared to 15 µg SC administration to elderly subjects ≥ 65 years in phase 1/2 clinical trial. <sup>4</sup>

Compared with the SC groups, both the single-dose ID group until 21 days after administration and two-dose ID group until 42 days, showed higher GMT for two strains of type A. (4) An additional report shows (2) the GMTs of each strain at 90 and 180 days after vaccination in the elderly subjects. The ID group showed a similar or better efficacy than the SC group until 180 days after vaccination in both the single-dose and the two-dose groups. In particular, the GMTs against B strain were remarkably higher in the two-dose ID group than in the two-dose SC group in elderly subjects (p = 0.006 at day 90, p = 0.013 at day 180). These results show that ID administration may induce immunity for a longer period than the general administration route. <sup>2</sup>

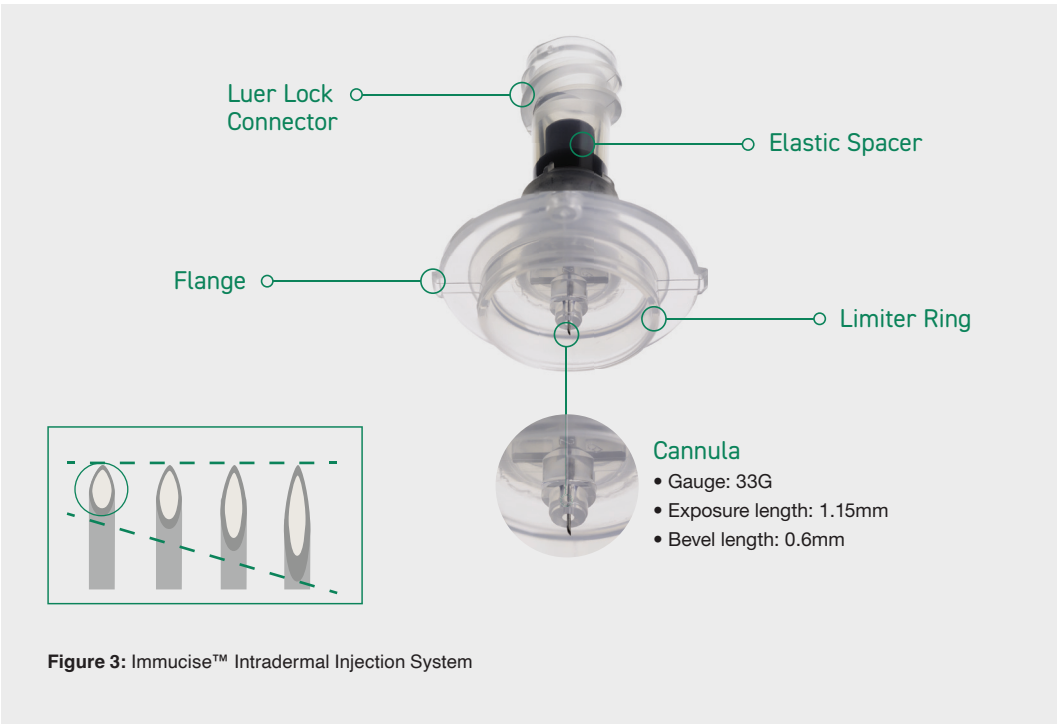


Figure 3: Immucise™ Intradermal Injection System

# Therapeutics

Beyond vaccines, intradermal delivery is being explored for the administration of biologics, and other drugs. <sup>6</sup> This method can improve the bioavailability and efficacy of these treatments. Intradermal delivery allows for localized administration, which can be beneficial for treatments targeting specific skin conditions or localized immune responses.

# Potential for Lymph Node Delivery

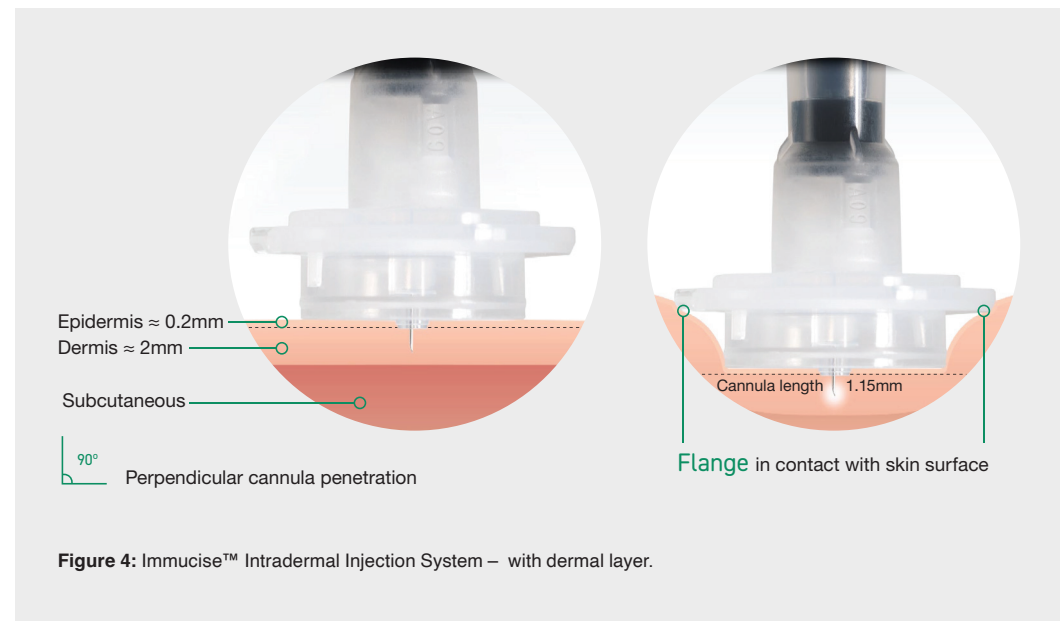
One of the most promising applications of intradermal delivery is its potential for targeted lymph node delivery, which may enhance immune responses and therapeutic outcomes.

Intradermal delivery can target lymph nodes by utilizing the rich network of lymphatic capillaries in the dermis. <sup>8</sup> Lymphatic capillaries are 10–60 µm in diameter, around three-times the width of blood capillaries. <sup>9</sup> They also have larger gaps between their endothelial cells compared to blood capillaries, which can expand to allow larger particles, such as proteins, lipids, and even pathogens, to enter the lymphatic system.

Furthermore, lymphatic capillaries are designed to absorb interstitial fluid, which includes particles and molecules that have leaked out of blood capillaries. Unlike blood capillaries, lymphatic capillaries have an incomplete, discontinuous, or absent basal lamina, (9) and overlapping endothelial cells, which can act like one-way valves to permit the uptake of larger particles. Due to their unique structure, particles with sizes of 10 to 100 nm are preferentially taken up by the lymphatics. <sup>10</sup>

## Further Promise for Intradermal Delivery

For immunotherapies, delivering therapeutic agents directly to the lymph nodes can enhance their ability to stimulate an immune response against cancer cells or other pathogens, and studies have explored the potential of intradermal delivery for targeted lymph node therapies, with promising results in cancer treatment.



Furthermore, ID administration immediately and efficiently delivers antibodies to lymph nodes, whereas little drug is delivered by systemic administration. (11)

Drug delivery to lymph nodes, achieved by changing the route of administration to ID, may improve drug efficacy, and ID administration of anti-PD-L1 antibodies has been found to significantly suppress tumor growth. (11)

Further research in this area is focused on developing methods to optimize the delivery of therapeutic agents to the lymph nodes, improving their efficacy and reducing side effects. Clinical trials are underway to evaluate the effectiveness of intradermal delivery for various therapeutic applications.

## Conclusion

Intradermal delivery has evolved significantly from its historic roots, with modern innovations like Terumo's Immucise™ Intradermal Injection System with the intention to offer enhanced precision and ease of use. Through broadening the application of this method to include a wider range of vaccines and therapeutic agents, intradermal delivery has the potential to revolutionize healthcare. Future research and development will continue to expand the possibilities of intradermal delivery, including its potential for targeted lymph node therapy.

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