Artykuł przeglądowy *Review*

Modern needle-free systems for livestock drug administration

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Summary

Needle-free drug delivery systems are a modern method of administering medications without the use of needles. These systems enable rapid and effective drug delivery, minimizing pain and enhancing both the safety and efficiency of treatment. Although their implementation may require initial investment from producers, needle-free technologies address many of the limitations associated with conventional injection methods, offering a safer, more cost-effective, and versatile alternative. Recent studies have shown that needle-free injection systems are as effective as traditional methods for animal vaccination. Furthermore, these systems may allow for reduced vaccine dosages without compromising immunological effectiveness. While needle-free systems do not directly reduce the use of antibiotics in livestock production, they may indirectly support this goal by facilitating broader vaccine coverage and improving the effectiveness of disease prevention. Their use also simplifies aspects of workplace safety and hygiene, for example by removing the need to handle needles.

Keywords: needle-free drug delivery, animal welfare, injection site lesions, carcass quality

Needle-free drug delivery systems have been used in many countries for over a decade. This technology offers numerous advantages that significantly improve the management of large animal herds. Compared to traditional injection methods, its main benefits include greater speed and ease of administration. Additionally, needle-free systems reduce stress and pain at the site of administration, thereby enhancing animal welfare. These systems also eliminate the risk of accidental needlestick injuries among workers, improving occupational safety. Furthermore, they can reduce the number of injection sites required, lower necessary drug dosage, and stimulate a stronger immune response (29, 33). A further concern with conventional syringes and needles is the risk of needle breakage within the tissue, which can lead to local tissue damage and persistent lesions at the injection site. The presence of broken needles in muscle tissue also poses a potential hazard to consumers. The application of needle-free delivery (NFD) technology mitigates these risks by preventing such injuries and minimising tissue changes following drug administration (24).

Possible routes of administration

To contextualize the discussion on modern needle-free drug delivery (NFD) systems, it is necessary first to review the conventional routes of drug administration commonly used in veterinary medicine. In this field, drugs are administered orally (via feed or water) or by injection, including subcutaneous (SQ), intradermal (ID), intramuscular (IM) and intraperitoneal (IP). The choice of the appropriate route of administration depends on the type of preparation, its volume, and the manufacturer's recommendations. Subcutaneous administration involves the injection of the drug into the fatty layer under the skin. In sows, the preferred injection site is located behind the ear, while in piglets, the 'tenting' technique is commonly used. This involves stretching the skin in the elbow or lateral area to facilitate drug delivery. Intradermal administration targets the dermal layer of the skin and is used for specific vaccines or medications that require local immune response stimulation. Intramuscular administration involves the delivery of the drug into muscle tissue. In pigs, intramuscular injection is typically performed in the neck muscles, just behind the ear, in accordance with standard practice. Injection into other muscle groups, such as the loin or ham, is discouraged or prohibited due to the risk of tissue damage and the potential impact on meat quality and food safety. Each route of administration has specific indications that ensure both therapeutic efficacy and the safety of animal-derived food products (18, 31). In cattle, subcutaneous injections are administered into the loose skin at the junction of the neck and shoulder. Intramuscular injection is given into the muscles of the thigh or the large muscles along the side of the neck (23).

Construction and types of needle-free systems

A needle-free injection system typically comprises three essential components: a reservoir, a nozzle, and a pressure source. The reservoir holds the injection fluid; i.e., the pharmaceutical preparation intended for administration. During the injection process, the nozzle is placed in direct contact with the animal's skin, serving as the conduit through which the drug is delivered into the body. The nozzle also regulates the diameter and velocity of the fluid jet, both of which are critical determinants of injection efficacy and penetration depth. The pressure source supplies the necessary energy – either mechanical, pneumatic, or gas-powered – to propel the drug through the skin without the use of a needle.

Based on the method of pressure generation, needle-free injection devices can be categorized into two main types. The first category includes spring-powered devices, in which pressure is generated by the release of a compressed spring upon activation of the piston. These systems are typically compact, cost-effective, and commonly employed for subcutaneous drug administration. However, their main limitation lies in the relatively low and fixed pressure output, which may restrict their applicability for certain formulations or routes of administration, thereby reducing their overall versatility.

The second type comprises compressed gas-powered devices, which typically utilizes carbon dioxide (CO_2), compressed air, or nitrogen (N_2) – the latter particularly in colder conditions (32, 40). These systems generate a consistent pressure output, offering greater flexibility and the capacity to deliver larger volumes of fluid compared to spring-powered devices. Compressed gas is stored in a reservoir and released at the moment of injection, providing increased force and precision during drug administration (28, 31).

Mechanism of needle-free injectors

Needle-free drug delivery involves the administration of a liquid substance beneath the skin using a high-velocity jet. The diameter of the nozzle through which the liquid is expelled is smaller than a human hair. This ultra-fine, high-pressure stream enables penetration of the skin, with the entire process taking less than 0.5 seconds. Specifically, the impact of a piston on the liquid reservoir generates a rapid increase in pressure, propelling the fluid at speeds exceeding 100 m/s. Upon contact with the skin surface, the jet creates a micro-opening that progressively deepens. As the injectable fluid accumulates, the velocity of the stream decreases, limiting further penetration. This method does not cause significant skin damage, as injection site reaches its final depth quickly, and subsequent impacts of the jet do not extend further. In needle-free systems, the drug disperses beneath the skin in a web-like pattern. The final distribution of the fluid depends on several factors, including the type of device used, the site of administration, skin thickness, the viscosity of the drug, and the pressure applied (18). In contrast, traditional needle-and-syringe administration results in the formation of a concentrated bolus at the tip of the needle within the tissue (13).

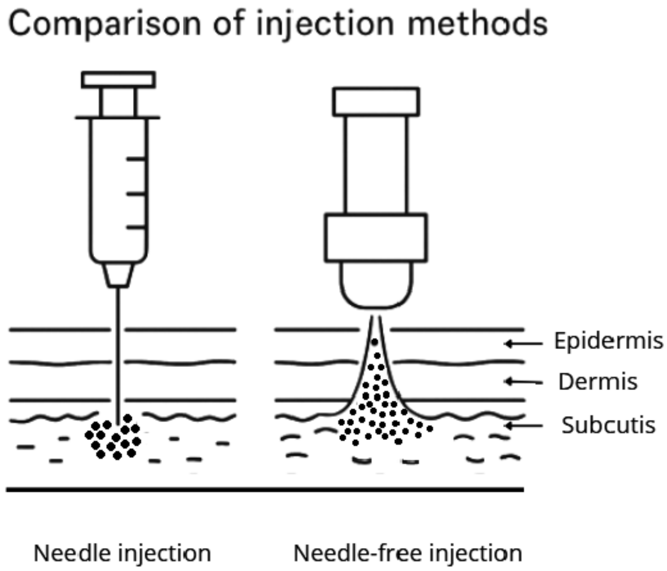

Fig. 1. Schematic comparison of the operation of a traditional needle-based system and a needle-free drug delivery system (original illustration by Julia Motławska)

Mechanism of immunological stimulation via NFD

In needle-free injection, the substance is dispersed in the intercellular space, allowing greater accessibility for immune cells, especially antigen-presenting cells (APCs). Immature dendritic cells, which are abundant in the skin and subcutaneous tissues, mature upon contact with an antigen and present it via MHC class II molecules, initiating a $CD4^+$ T cell-dependent immune response. Additionally, antigens delivered in this way can also be processed and presented via MHC class I molecules, leading to the activation of $CD8^+$ cytotoxic T cells. The improved immune reaction observed with needle-free delivery is due to this enhanced accessibility – not a different mechanism of immune activation. This suggests that needle-free delivery not only enhances the quality of the immune response but also allows for a reduction in the amount of antigen required (2, 3, 19).

Method of drug administration and animal welfare

Modern approaches to animal husbandry increasingly emphasize the importance of improving animal welfare, particularly by reducing stress associated with conventional drug administration methods. Traditional injections can induce stress-related behaviours, such as vocalisation, increased agitation, or reduced feed intake: effects especially common in pigs. Needle-free drug delivery systems represent a promising alternative, as they have the potential to minimize the stress responses typically observed during conventional injections.

A study conducted by Lewis et al. (22) evaluated the effects of traditional injections and needle-free drug delivery methods on stress responses in pigs. In this study, pigs were vaccinated using two approaches: traditional intramuscular injection and subcutaneous administration via needle-free devices. Animal behaviour was monitored at two time points – one hour and 24 hours after vaccination. The findings indicated that traditional injection methods, particularly IM administration, elicited significantly stronger stress responses compared to the NFD approach. Piglets vaccinated using the IM method exhibited more pronounced vocalisation and behavioural signs of anxiety, such persistent movement within the pen, interpreted as responses to pain and stress associated with needle penetration. In contrast, piglets vaccinated via the ID needle-free method demonstrated less vocalisation and more natural behaviours. These animals also showed reduced aggression and a greater willingness to drink and feed within 24 hours of vaccination. Moreover, the study reported greater weight gain in piglets vaccinated using the needle-free system compared to those injected with a conventional needle and syringe (22). Stress induced by needle injections has also been associated with decreased appetite and over time, delayed growth, which may negatively impact production performance (12). These findings suggest that NFD technology may offer advantages not only in terms of animal welfare but also with regard to health and productivity, facilitating faster recovery following vaccination (22).

Overall, intradermal drug administration in pigs has been positively received. Notably, studies investigating the IntraDermal Application of Liquids (IDAL) have demonstrated that this method may reduce fear and pain responses in sows compared to conventional needle and syringe vaccination. Additionally, no adverse skin reactions were observed at the injection site 28 days post-vaccination. Sows vaccinated with the IDAL system also exhibited lower levels of C-reactive protein (CRP) compared to those vaccinated using traditional methods, suggesting a reduced inflammatory response. Furthermore, IDAL vaccination may help prevent long-term muscle damage commonly associated with intramuscular injections, thereby contributing to improved animal welfare (38).

Other studies have evaluated the pain response caused by injections in livestock (5). One such study was conducted on young Saanen kid goats less than 10 days old, with the aim of assessing both the level of pain experienced by the animals and the effectiveness of three different anaesthesia methods, which varied in form and application technique. The kids were randomly assigned to five experimental groups. All animals underwent a series of skin punctures around the horn buds using a needle, followed by the application of one of the following: a topical anaesthetic cream (TA), a vapo coolant spray (VS), a topical anaesthetic agent delivered using a needle-free injector (JI). In the control group (C), no anaesthetic was administered, but a pain response was elicited through puncture. In the final group (sham), neither anaesthetic nor painful punctures were applied – only gentle contact with the previously punctured sites was performed. Throughout the experiment, heart rate and vocalisation were monitored during both the puncture phase and the administration of anaesthesia. The most favourable results were observed in the JI group, where the pain response was reduced by 96% compared to the TA group. The motor responses of the kid goats during the procedure was reduced by 83% compared to the other treatment groups, indicating a significantly lower pain response. This finding was further supported by heart rate measurements, which were lowest in the needle-free injector (JI) group. Notably, the study's design allowed for the evaluation of various needle-free methods and forms of anaesthetic administration under consistent conditions, providing a reliable comparison of their effectiveness (5). The use of traditional needles has been shown to significantly increase stress levels in farm animals, as demonstrated in a study by Dalmau et al. (6). This stress is strictly manifested through elevated heart rate, increased vocalisation, and heightened motor responses during injection procedures. In contrast, needle-free drug administration not only reduced these adverse reactions but also facilitated a more uniform distribution of the anaesthetic, further enhancing its efficacy.

Importantly, NFD vaccination did not cause any visible signs of long-term stress, such as reduced feed intake, feeding frequency, or significant changes in social behaviour – symptoms often associated with traditional injection methods. This study confirmed that needle-free injection systems have considerable potential as a beneficial alternative to conventional injections, not only by reducing stress in animals but also by enhancing overall animal welfare. It is noteworthy, however, in human medicine, NFD vaccination techniques are sometimes associated with increased pain perception compared to traditional methods (17). Additionally, local reactions such as pain, swelling, or redness tend to occur more frequently, following NFD vaccination (25, 41).

Comparison of the efficacy of traditional and needle-free injection systems in mass animal vaccination and drug administration

Numerous studies have compared the efficacy of needle-free injection systems with traditional needle-and-syringe methods during mass preventive vaccination programs (18, 27, 30, 33, 40). For example, when calves were vaccinated with an anatoxin against *Clostridium chauvoei*, both methods elicited comparable immune responses, with similar antibody levels observed in both warm and cold seasons (18, 28). Other studies demonstrated that antibody titers following vaccination of calves against bovine viral diarrhoea virus (BVDV) and infectious bovine rhinotracheitis virus (IBRV) using modified live vaccines did not differ significantly between animals vaccinated with needle-free devices and those vaccinated using traditional methods (33). NFDs have also been successfully employed in vaccination against bluetongue virus (BTV) (27) and have been used experimentally for vaccination against foot-and-mouth disease (FMD) (40). In one such study, several dozen heifers were randomly assigned to three equal groups. The first group received a 2 mL dose of vaccine subcutaneously via a conventional needle and syringe. The second group received the same volume using a CO_2-powered needle-free device. The third group received a 1 mL dose intradermally using the same device. Antibody titers measured 120 days post-vaccination were comparable across all groups, indicating that needle-free delivery systems provide similar efficacy in FMD prevention. Additionally, the automatic needle-free injection (ANFI) method was found to be completely safe. Based on these findings, the authors suggested that needle-free intradermal vaccination may allow for dose reduction without compromising efficacy (40).

Numerous studies have been conducted across various livestock species to compare the effectiveness of needle-free and traditional injection methods in stimulating immune responses. Antibody levels were measured following vaccination against various pathogens, providing a basis for assessing the efficacy of each technique. For example, heifers aged 4-6 months vaccinated with the *Brucella abortus* RB51 strain at a dose of 1010 CFU showed comparable antibody levels regardless of the vaccine administration method (30). Similarly, in 5-10-month-old Holstein heifers, no significant differences in antibody titers were observed following vaccination against infectious bovine rhinotracheitis (IBR), Mannheimia haemolyitca (MH), and Leptospira Pomona (LP), regardless of the technique employed. However, in 5-10-month-old Holstein steers, the antibody response to IBR was higher in animals vaccinated using the NFD, while the response to LP remained unaffected by the administration method. In another study, Van Drunen Little-van den Hurk (7) reported the vaccination of cows with bovine herpesvirus-1 (BHV-1) glycoprotein-C (gC) using the Biojector 2000 needle-free system (Bioject Inc.) resulted in a significantly stronger immune response, as evidenced by elevated levels of anti-gC antibodies. These findings suggest that the injection method can influence the magnitude of the immune response. However, other factors – such as the sex of the animal (14) and the specific antigen being measured (1) – also play a significant role. Similar outcomes have been reported in studies involving rabbits (1), sheep (26), and pigs (15). Additionally, research in one-year-old bulls demonstrated that the immune response to IBR was stronger following needle-free vaccination compared to the traditional injection, while the response to MH remained consistent across both techniques (14).

Houser et al. (15) conducted a study involving 130 pigs vaccinated against pseudo rabies virus (PRV) and *Mycoplasma hyopneumoniae*. The animals were divided into three groups: the first group received injections using a traditional needle and syringe; the second group was vaccinated using an air-powered needle-free transdermal injection system; and the third group served as unvaccinated controls. Both injection methods elicited a comparable and satisfactory serological response to the vaccine.

Several studies have compared the efficacy of vaccination using NFD systems and traditional injection methods under varying climatic conditions, particularly to assess the performance of NFD systems in the cold Canadian climate. These investigations were prompted by the requirement to replace CO_2 with N_2 in NFD systems at low temperatures, a modification that could potentially vaccine efficacy. The findings indicated that the use of nitrogen as applied in BI systems ensured satisfactory performance under cold conditions. Additionally, the incidence of local reactions was found to be influenced by ambient temperature and season. Notably, animals vaccinated in autumn exhibited a slightly different immune response compared to those vaccinated in other seasons, likely due to variations in maternal antibody levels, environmental conditions, and feed composition (31, 32).

In addition to their application in vaccine delivery, needle-free systems have also been employed for the administration of other pharmaceutical agents. One such example is the use of needle-free injectors (NFI) for iron supplementation in piglets. In a comparative study evaluating the efficacy of iron preparations administered via conventional intramuscular injection versus a needle-free system, no significant differences were observed in haemoglobin and haematocrit levels between the two groups. These findings suggest that needle-free systems may represent an effective alternative to traditional methods for delivering iron supplementation in piglets (39).

Needle-free injection systems have also been employed for the administration of sex hormones in cows in the reproductive management of both dairy and beef herds. Notably, Leslie et al. (20, 21) reported on the use of this technology for the administration of cloprostenol. Moreover, studies have demonstrated that needle-free systems can effectively deliver local anesthetics during castration procedures. Specifically, needle-free administration of lidocaine in Holstein bulls and pigs provided comparable physiological and behavioral outcomes to traditional needle injections, indicating sufficient analgesic efficacy (4, 36).

Injection site lesions and carcass quality

Some studies have provided insightful observations regarding local reactions following injections administered either with needles or using needle-free systems (24, 32). For example, research conducted on Angus bulls comparing reactions after BVD vaccination reported only mild local swelling at the injection site. Interestingly, these reactions were more pronounced in the group treated with needle-free systems, which the authors attributed to the high pressure employed in such devices. Histological examinations revealed changes in the muscle and fat tissues in both groups; however, these were considered negligible in terms of their impact on meat quality (24). Similarly, Rey et al. (32) observed a higher frequency of skin reactions at the injection site with needle-free injectors. In contrast, Eun Young Ko (9) reported different results in a study investigating post-injection changes following foot-and-mouth disease vaccination in pigs. The incidence of lesions in the ham was 14.82% lower in pigs vaccinated with needle-free injectors compared to those vaccinated using traditional needles. These findings pertain to intramuscular injections.

Moreover, parenterally administered pharmaceuticals can affect deeper tissues, including muscle layers, potentially exerting a considerable influence on carcass quality. Traditional needle-based injection systems can cause tissue damage at the injection site, resulting in post-mortem tissue alterations that may diminish the commercial value of the meat. Post-injection lesions are a major quality defect in meat, necessitating the removal of muscle fragments and negatively affecting the tenderness of the surrounding muscles (8, 10). Muscles damaged by drug administration may be deemed unfit for consumption and disqualified during the production stage, leading to significant economic losses. There is also a risk of broken needles remaining at the injection site, which requires the use of metal detectors in processing plants. However, some needles or fragments may remain undetected, posing a serious food safety risk (35). Needle-free injection systems eliminate the risk of needles or fragments being left in carcasses. They also appear to reduce or eliminate injection site lesions resulting from the use of contaminated needles (14). Traditional administration of drugs with a needle and syringe causes a bolus to form in the tissue surrounding the needle tip. This does not occur with needle-free injection, which results in a more even dispersion of the drug and causes less damage to muscle tissue (13). Some studies have shown that the incidence of lesions in the ham of pigs vaccinated with a needle-free injector was 14.82% lower than in control pigs (9). Minor changes in muscles and lymph nodes, which were not significant for carcass quality, were reported following the administration of vaccine against pseudorabies virus (PRV) and *Mycoplasma hyopneumoniae*. No abscesses or granulomas were observed during post-mortem examinations. In studies conducted by Houser et al. (15), in which PRV and Mycoplasma hyopneumoniae vaccines were administered using both traditional needles and needle-free injection systems, microscopic changes were observed in 2.3% and 1.5% of pigs, respectively. Therefore, no significant difference was found in the incidence of serious or histological changes at the injection sites of pig carcasses between the needle-free and traditional vaccination techniques.

There are studies indicating a risk of abscess formation in pig muscles as a result of injuries caused by drug administration using both of the above methods.

For example, in pigs, a common pathogen responsible for abscess formation at injection sites is *Arcanobacterium pyogenes*. Gerlach et al. (11) conducted a study in which injections were administered to piglets in the neck and ham muscles: on one side of the body using needles and syringes, and on the other side using a needle-free jet injection system. The skin of the piglets was previously contaminated with an inoculum of *Arcanobacterium pyogenes*. After euthanasia, the piglets were dissected, and the tissues showing post-injection changes in the form of abscesses were subjected to histopathological evaluation. Surprisingly, the study did not demonstrate any significant advantage of needle-free systems, confirming a high risk of microbial penetration from the skin surface into the tissues and subsequent abscess formation. The tissue response to the adjuvant was also evaluated. Notably, no significant differences in granulation tissue formation at the injection site were found between the needle and needle-free injections. Similar results were reported by Sutterfield et al. (37), who observed that NF injections may promote greater penetration of microorganisms, such as *Escherichia coli* (*E. coli*), into muscle tissue. In their study, the use of the NF technique resulted in an increase of 0.5 log10 CFU/g in *E. coli* colonies in the *longissimus dorsi* muscle compared to traditional needle injections. These studies suggest that vaccina-

Tab. 1. Comparison of traditional needle-based systems and needle-free delivery systems for drug administration in livestock

Criterion	Needle injection	Needle-free injection system (NFD)
Administration technique	Needle and syringe	Stream injection under pressure
Risk of microbiological contamination	Possible – mainly via contaminated needles	Possible – via introduction of skin pathogens
Local reactions	Swelling, redness, pain, histopathological lesions	Minor skin damage, less muscle tissue damage
Impact on carcass quality	Risk of muscle damage; presence of needle fragments	Lower incidence of lesions, no risk of retained fragments
Animal stress and welfare	Higher stress, strong vocalization, decreased appetite	Lower stress levels, maintenance of appetite and normal behaviour
Immunological effectiveness	High, well-documented	Comparable or higher (depending on antigen and technique)
Possibility of dose reduction	Rare	Often possible with intradermal vaccination
Risk of personnel injury	High (needle-stick injuries, occupational exposure)	Low (no sharp waste)
Initial cost	Low (inexpensive equipment)	High (cost of equipment and training)
Administration time	Longer	Shorter; allows automation
Application in mass vaccinations	Labour-intensive	Greater efficiency, improved ergonomics, time-saving
Retention of foreign body	Yes (needle fragments)	No (no elements)
Safety for meat (metal detection)	Required	Not required
Device universality	Universal (syringe + needle fits most)	No universal devices; may require specific equipment per drug
Needle disposal	Required (biohazard risk)	No need to dispose of needles

tions administered using NF techniques may be associated with a higher risk of introducing microorganisms present on the skin or hair of animals, such as *E. coli* or *Arcanobacterium pyogenes*, into the tissues, resulting in more local reactions and abscess formation than with needle-based systems.

Overall, although needle-free injections do not cause direct muscle damage, evidence indicates that both needle and needle-free drug administration carry a risk of introducing microorganisms from the animal's body surface into the tissues, potentially leading to abscess formation at the injection site and causing serious carcass defects.

Intramuscular administration of drugs using needles may also lead to a reduction in meat quality by decreasing its tenderness. In particular, injectable antibiotics are associated with an irritating effect on tissues, which is related to both the action of the antimicrobial substance itself and the vehicle, such as polyethylene glycol or propylene glycol (8). Dubeski et al. (8) conducted three experiments to assess the effect of intramuscular injections on beef tenderness. Shear force measurements were used as the method for evaluating tenderness. In the first group, calves were given vaccines containing clostridial toxoids (Blacklegol® Covexin® 8, Ultrabac®); the second group received three different commercially available antibiotics (Nuflor®, Trivetrin™, Excenel®); and the third group was administered two vaccines against respiratory infections (Bovishield™ 4, Pyramid™ MLV 4). Veterinary preparations were injected intramuscularly into the thigh muscle on one side of the body, while a saline solution was injected on the opposite side. Injections were administered without prior disinfection of the injection site.

The injection of 5 ml of saline solution did not cause any significant changes. In contrast, the lesions caused by clostridial toxoids were extensive and penetrated deeply, affecting a considerable area of the semimembranosus muscle. The changes following antibiotic administration were moderate in size, while those resulting from vaccine administration were very small and would likely not have been detected during processing, due to both their small size and inconspicuous appearance. All preparations used in the experiment caused an increase in shear force at the site of the post-injection lesion and at a distance of 2.5 cm from the lesion, indicating that the tenderness of the meat was significantly reduced as a result of the intramuscular administration of veterinary preparations.

In summary, several studies have compared post-injection changes in meat resulting from the use of needle and needle-free systems. However, the results are inconclusive and warrant further investigation.

Disadvantages associated with the use of needle-free systems

certain disadvantages of needle-free systems include higher initial costs related to the purchase of equipment, the need for staff training, and the challenge of gaining staff and owner confidence in the effectiveness of these systems (28, 34). However, a long-term cost analysis showed significant labour savings due to shorter injection times. The use of a needle-free injector resulted in an annual cost reduction of $ 1,161 (16).

Needle-free drug delivery systems represent a promising alternative to traditional needle injections. Their primary advantages include minimising the number of punctures, reducing stress in animals, and enhancing the effectiveness and safety of therapy. Numerous studies confirm their usefulness in mass vaccination programs and livestock health management. Additionally, needle-free technologies contribute to improved animal welfare, health, and production performance.

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