

**Post-injection Complications. Nicolau Syndrome as a Consequence of Local Irritant Effects of Drugs, Including Antiseptics, Local Anesthetics, NSAIDs, Steroids and Anticoagulants****Abstract:**

It has been shown that some drugs considered to be of good quality today can cause an iatrogenic disease known as Nicolau syndrome. Nicolau syndrome is a rare cutaneous drug reaction occurring after injection many drugs. This disease has been found to be caused by the very strong local irritant activity of drug solutions. It turned out that the standard for assessing the quality of drug solutions does not include assessment of their osmotic activity and the strength of their local irritating effect on various tissues during injection. At the same time, drug solutions produced by different pharmaceutical companies may contain, in addition to the main ingredients, other ingredients (hydrochloric acid, sodium hydroxide, propylene glycol, etc.). Very often the additional ingredients increase the osmotic activity of the drug solution, which is not controlled today, so it remains unknown. This is why drug solutions produced by some pharmaceutical companies can have hypertonic activity, which can sometimes by ignorance reach values that are incompatible with the vital activity of human body tissue cells. Therefore, injections of such drug solutions can have a very strong dehydrating effect on the tissue cells at the injection sites, have a local irritating and cauterizing effect. It has been shown that even steroid solutions in some manufacturers may have excessive hypertonic and acidic activity, which gives them a local irritating effect. This is why in some cases the injection of a steroid solution does not eliminate, but rather increases local inflammation and causes necrosis. Therefore, to exclude postinjection necroses and abscesses, it is proposed to include an assessment of the osmotic activity and local irritant effect of drug solutions in the drug quality control standard and to prohibit the injection of drug solutions with excessive hypertonic activity.

**Keywords:** drug quality; drug solutions; osmotic activity; acidic activity; irritant activity; necrosis; abscess.

**1. Introduction**

It is no secret that the essence of many diseases boils down to inflammation of "diseased" areas of the body or that inflammation accompanies one or another "disease". This is why patients complain about the symptoms of inflammation, like local soreness, hyperthermia, swelling and redness. In this regard, the traditionally prescribed analgesics, antipyretics : local anesthetics, steroids and non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for treating local and systemic inflammation.. Steroids are prescribed in different formulations like ointment and suspensions for the treatment of many inflammatory conditions like dermatitis, conjunctivitis vaginitis; and other joint diseases like bursitis, periartthritis, keloids, sciatica, Dupuytren's contracture and others) [1-4]. Nevertheless, contrary to their name, each of these remedies can cause iatrogenic disease, representing local inflammation of unclear pathogenesis.

Therefore, there is still a lack of consensus among researchers about the efficacy and safety of all of these groups of drugs, including steroids and NSAIDs [5-9]. Further, it is well known fact that reports of post injection inflammations, infiltrates, necrosis, and abscesses continue to appear despite the preventive measures. At the same time, it seems paradoxical that these post injection complications occur with equal frequency after injections of drugs from different pharmacological groups, including steroid and NSAIDs. Nor does its name, Nicolau syndrome, bring clarity to the understanding of the etiology and pathogenesis of this iatrogenic disease [10-12]. For about 100 years, the cause of this iatrogenic disease remains unknown.

Nicolau syndrome was described in the early 1920s by Freudenthal and Nicolau as a local complication following intramuscular injections of Bismuth salts for the treatment of syphilis [13]. Nicolau syndrome is manifested by local soreness, aseptic inflammation, infiltration, tissue necrosis at the injection site (skeletal muscles, other tissues, subcutaneous fatty tissue and skin), as well as erythema and hemorrhagic stain in the skin at the injection site. In 2 to 3 days a post-injection abscess develops in this place, and then a scar. Since then, several reports have appeared in the literature about this disease, which occurs after intramuscular, intra-articular, intravenous, subcutaneous and other injections of steroids, NSAIDs, antihistamines, penicillins, antiseptics, anticoagulants and many other drugs [14-16].

Of note is the fact that **Nicolau** syndrome is characterized by the development of acute inflammation at the injection site. In particular, two clinical cases of acute Nicolau syndrome have been reported following intramuscular injections of the corticosteroid acetone triamcinolone [10]. In addition, it is reported that from 2005 to 2009, a committee of medical experts and a mediation board in Germany reviewed 1,528 cases of suspected therapeutic errors related to steroid injections. At the same time, 278 cases were identified in which local complications occurred after topical glucocorticosteroid injections. The injections were administered intraarticular, paravertebral, intramuscular, and elsewhere [17]. The cause of local complications could not be determined.

It becomes clear that local post-injection complications can develop when drugs injected into any tissue (skin, subcutaneous fatty tissue, any other tissue, skeletal muscle, scar tissue, etc.). It also becomes clear that Nicolau syndrome can develop from the injection of any drug, from any pharmacological group. It has been shown that in most cases, Nicolau syndrome develops in the first few minutes after injection. At the same time, clinical guidelines on drug injection still do not include monitoring of tissue dynamics immediately after drug injection [17]. Therefore, the local postinjection safety of drug solutions is still low. At the same time, post injection drug safety remains an understudied area of clinical pharmacology.

## **2. Sources of the problem**

Currently, drugs in the dosage form "Solution for injection" are widely used for hospital treatment of all diseases in adults and children. The place for injection into the patient's body is traditionally determined by the specific pharmacokinetics and pharmacodynamics of the selected drug, as well as the localization and type of the existing pathological process. Previously, injections of drugs were made only in healthy tissues. In recent years, recommendations on the advisability of injecting drugs into pathologically altered tissues have appeared. Therefore, it is of scientific interest to evaluate the local efficacy and safety of drug injections not only in healthy tissues but also in pathologically changed tissues. For example, the drug efficacy can be tested while injecting steroids into the area of hemangiomas, strictures and keloid scars [2-6].

Despite the described promising results of injecting drugs into "inflamed" areas of the body, postinjection complications have been established in the clinic. For example, the complication rate after steroid injection has been reported to be 7% with a higher incidence of local complications compared to systemic complications [7]. Therefore, the risk of local postinjection complications is a limitation for the routine clinical use of injections of any medication, including steroids.

Corticosteroid injections into inflamed areas of the body have been reported to be a treatment that has been used for decades with good effect. However, steroid injections sometimes increase local inflammation and cause necroses and abscesses [17,18]. These complications have been reported to occur after steroid injections into skeletal muscles, under the skin, in the jaw, in the sole of the foot, in the tendon spaces, inside the joint, eyes, and in the spine [19-22]. Most of these individual cases involved mild, mostly cosmetic, complications. Some of them included more extensive manifestations in the form of drug-induced skin embolism and severe tissue necrosis in Nicolau syndrome. Nicolau syndrome is thought to be caused by acute arterial thrombosis or spasm during intravascular injection of an insoluble drug [17]. Therefore, antispasmodics, heparin, and other anticoagulants have been tried to prevent postinjection complications, but without success.

In addition, another complication of steroid injection has been described: Tachon's syndrome [23-25]. It is thought that Tachon's syndrome may be a venous analogue of Nicolau syndrome (corticosteroid injection into an artery). It is reported that of 500 French rheumatologists interviewed, 92 rheumatologists reported 318 cases of Tachon's particular pain syndrome following injections into the lumbar epidural space (39%), upper extremity (30%), lower extremity (mostly heel) (24%), or other sites (7%). The reported that Tachon's syndrome was caused by the following steroids: cortivasol (67%), hydrocortisone (25%), betamethasone (7%), or parametasone (1%). Symptoms occurred 1-5 minutes (78%) or less than 1 minute (22%) after injection, and acute axial pain usually lasted less than 5 minutes (34%) or 5-15 minutes (51%). In addition to lumbar (84%) and/or spinal (25%) pain [often preceded or associated with chest pain (36%)], other symptoms were: restlessness (87%), shortness of breath (64%) facial flushing (64%), diffuse sweating (41%), agitation (29%), temporary cough (23%), abdominal pain (20%), transient hypertension (15%), pallor (10%), hypotension (8%), diarrhea (3%) and headache (3%). None of these patients were known to have allergies, and only 2% developed urticaria. The outcome was favorable in all cases [24].

The search for the causes of Nicolau syndrome and Tachon syndrome has led researchers to the following conclusion. It is believed that the drug causing the local postinjection complication is usually a single corticosteroid (or a single antibiotic), or a combination of a corticosteroid with a local anesthetic (or a combination of an antibiotic with a local anesthetic), or a combination of a corticosteroid with a nonsteroidal anti-inflammatory drug. In addition, it is widely believed that in cases of extensive tissue necrosis, especially in the buttocks, the cause of postinjection complications is a short injection needle, the end of which did not reach the muscle and, therefore, the drug solution did not penetrate the muscle. Therefore, it is suggested to use a long injection needle to increase injection safety. In addition, it is believed that to prevent postinjection necrosis and abscess, a local anesthetic should be injected first before a steroid, antibiotic, or other drug is injected [17]. Thus, the cause of the development of post-injection necrosis and abscesses remains unknown to the end, so we cannot completely exclude Nicolau syndrome when injecting modern drugs.

However, in recent years, the cause of post-injection inflammation, necrosis and abscess has finally been established. It has been shown that the cause of Nicolau syndrome is a very

strong local irritating effect of medicinal solutions [26]. This became possible because the local irritating effect of drugs on tissues at injection sites is not controlled, as it is not included in the standard of drug quality control [27]. It has been shown that in addition to this, the standard for quality control of medicines does not include an assessment of their osmotic activity [28]. In addition, it has been shown that the drug quality control standard allows for the presence of high acidic or high alkaline activity in some medicinal solutions [26-28]. It is reported that drug solutions considered to be of high quality today may have isotonic and weak alkaline activity, but sometimes (in some serial numbers or in some pharmaceutical companies) drugs by chance (by ignorance) may have hypotonic or hypertonic activity, high acid or alkaline activity, as well as a strong local irritant effect, which in some cases, it can transform into a cauterizing effect [26]. In experiments on pigs, it was shown that dilution of medicinal solutions several times with water for injection to impart isotonic activity completely prevents the development of Nicolau syndrome with subcutaneous injections [28,29].

The discovery of this cause for the development of post-injection complications became possible use of information about the manufacturer of the drug (pharmaceutical company), the date of manufacture of the drug, the batch number, the formulation of the drug, physical-chemical indicators of the quality of the drug solution, in particular, the concentration of all ingredients, the pH value and osmotic activity of the drug solution [26-28].

It is reported that the standard of quality control of medicines does not include control of osmotic activity, as well as local dehydrating and irritating effects of drugs [26]. Therefore, some injection solutions that are currently considered high-quality may not have isotonic activity. Studies have shown that this is indeed the case and a significant part of the drugs have hypotonic or hyperosmotic activity [26]. A study was conducted on the osmotic and acidic activity of high-quality injection solutions of drugs and their post-injection safety. It is reported that one part of the medicinal solutions has very low osmotic activity (is hypotonic solutions), the other part of the solutions has osmotic activity of about 280 – 300 mosmol/l of water, and the third part of the drugs has osmotic activity exceeding the norm by 2 or more times (is hypertonic solutions). At the same time, medicinal solutions with hypotonic and isotonic activity do not cause post-injection necrosis and abscesses, medicinal solutions with excessively high hypertonic activity (2 or more times more than isotonic activity) cause post-injection inflammation, necrosis and abscesses [28]. In this regard, the researchers draw attention to the fact that the osmotic activity of medicinal solutions requires special attention from pharmaceutical companies, drug consumers and researchers.

### **3. Controlled and uncontrolled physical-chemical properties of drug solutions. Osmotic activity.**

In accordance with the Pharmacopoeia, the existing drug quality control standard includes the control of many physical-chemical properties [30]. Based on this, no one questioned the quality of medicines that passed the standard test. Therefore, it was generally accepted across the globe that high-quality medicinal solutions are safe. In particular, it was considered certain that all drugs ready for injection have a pH of 7.4 and are isotonic. Therefore, researchers around the world did not pay attention to the first reports that the physical-chemical properties of many medicinal solutions, considered to be of high quality, are the cause of their local aggressive action on plasma and shaped blood elements. At the beginning of the 21st century, it was shown that the local effect of drugs in the dosage form of "solution for injection" on plasma and blood cells is non-specific and depends on local interaction factors such as acid (alkaline) activity, osmotic activity and temperature of drug solutions [26-28]. Currently, the results of independent studies have begun to appear, which have confirmed that the quantitative and qualitative characteristics of medicines in the dosage form of "solution for injection" distinguish drugs from

different manufacturers from each other and underlie the difference in their local effect on blood during intravenous injections [31,32].

Thus, reports have recently appeared showing that often the local action of drugs is determined not only by their specific pharmacological action, but also by their nonspecific activity, which depends not so much on the main ingredient (the main drug) as on the physical and chemical properties of the drug form (in this case, the solution for injection). In this regard, to understand the mechanism of local drug action during injection, it is completely insufficient to have information only about the name of the drug (the main ingredient) and its dose. It is reported that in order to understand the peculiarities of local drug action, it is very important to consider such physicochemical properties of the drug solution as the pH value, the osmotic activity value and the local tissue temperature at the injection site [29]. Since all drugs in different batches and from different manufacturers have different physical-chemical properties, the role of acid and osmotic activity in post-injection complications can be established only by taking into account the pharmaceutical company that produced the drug, the date of drug manufacture, batch number, drug formulation, the concentration value of all ingredients dissolved in the solution, the pH value, the osmotic activity value of the ready solution and other quality parameters of a drug from a certain party only [26-29]. **The fact is that not every pharmaceutical company produces patented drugs strictly under the license of patent holders. Some pharmaceutical companies do not produce drugs under license. At the same time, pharmaceutical companies change the formulation of their drug in order to avoid liability to the owner of the patent and/or license for the drug. Changing the formulation of a drug automatically changes many of its physical-chemical properties. Since part of the physical-chemical properties is included in the list of controlled physical-chemical indicators of drug quality (in accordance with the requirements of the Pharmacopoeia), part of the physical-chemical properties of drugs is controlled and indicated in the passport (certificate) of drug quality. However, osmotic activity is not included in the list of controlled indicators of drug quality, so it can be any. It is quite appropriate to add that the pharmaceutical company changes not only the formulation, but also the name of the drug.**

Unfortunately, many researchers ignore the quality indicators of drugs in their studies. Only a few researchers include the name of the pharmaceutical companies whose drugs caused postinjection complications. As an example, we can point to a report of a postinjection complication that included information about the proprietary name of the drug and the pharmaceutical company that manufactured the drug, namely triamcinolone acetonide 40 mg/mL (Kenalog®; Bristol-Myers Squibb SRL, Anagni, Italy) [33].

However, the bulk of reports noting local postinjection complications following drug injections are limited to only specifying the main active ingredient and its single dose (triamcinolone, betamethasone phosphate sodium, methylprednisolone, dexamethasone [34-43]. There are also many other reports in which the quantitative and qualitative characteristics of drugs injected that caused local complications are incomplete and inaccurate [44-46].

There are very few reports indicating the significance of certain physicochemical properties of drugs produced by different pharmaceutical companies. Such an example would be a report in which it was shown that when injected into the vitreous body, the local effect of a suspension of triamcinolone acetonide produced by different pharmaceutical companies differed from each other and depended on the physicochemical properties of the drugs. Specifically, Kenalog 40 (C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub> MW: 434.50; Bristol Myers Squibb, Princeton, New Jersey) was reported to have a pH of 5.76, Tricense (Tricense; Alcon Pharmaceuticals, Fla. Worth, Texas) had a pH of 6.90, and Transition (C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub> MW: 434.50; Kunming Lidu Pharmaceutical Company, Ltd.,

Yunnan, China) had a pH of 6.79. In addition, it was reported that all these suspensions of triamcinolone analogue had crystals of different sizes and ratios. The results of the experimental study showed that the local action of the 3 triamcinolone acetonide analogues depended on the physicochemical properties of the specific drugs [47].

In 2012 a study of the acidic (~~alkaline~~) activity and osmotic activity of high-quality solutions of 200 drugs from various pharmacological groups and from various pharmaceutical companies were conducted. The results showed that the vast majority of medicinal solutions manufactured for injection had a pH value below 7.0 and an osmotic activity value above or below 280-300 mosmol/l of water [48]. In other words, most of the high-quality solutions for injection were not alkaline, but acidic. In addition, a very large part of the medicinal solutions had hypotonic or hypertonic activity.

This was followed by a thorough investigation of exactly what causes the local irritant effect of the drugs. For this purpose, the pH value, the osmotic activity value, and the ingredients of the drug solutions were taken into account [49,50]. The results confirmed that some drugs considered to be of high quality may have a local irritant and inflammatory effect on the tissue at the injection site because they are acidic rather than alkaline (46). It has also been confirmed that the local irritant effect of acidic drug solutions is manifested by local tissue inflammation and local skin hyperthermia at the injection site. Therefore, it was suggested to use a thermal imager to visualize local hyperthermia [51,52]. These reports confirmed that local tissue inflammation at the site of acidic drug injection occurs within the first seconds after injection and is most often local inflammation of a reversible nature, and then disappears without a trace after a few minutes. Only if the drug solution has both acidic and excessive hypertonic activity, the injection causes development of post-injection inflammation infiltration, tissue necrosis and abscess.

Additionally, there were reports stating that high hypertonic activity of drug solutions can be an independent cause of local irritation and postinjection inflammations, necroses and abscesses [26,29]. Using the example of antibiotic solutions, it was found that hypertonic activity had solutions that had ingredients with a total concentration of more than 5%, but post-injection necroses and abscesses were caused by drug solutions that had a total concentration of all ingredients greater than 10% [53]. In parallel, hypertonic activity was found in drug solutions of some antiseptics, nonsteroidal anti-inflammatory drugs, steroids, antibiotics, radiopaque contrast agents and salts of alkali metals, which are considered to be quality and ready for injection today. In experiments on piglets, it has been shown that injections of hypertonic solutions of these drugs cause post-injection complications in the form of aseptic inflammation, necrosis and abscess. At the same time, preliminary dilution of these hypertonic solutions with water for injection up to giving them isotonic activity, eliminated their local irritating effect during subcutaneous injections and excluded the development of postinjection necroses and abscesses [26].

Further in an experimental study on piglets, the dynamics of local skin temperature at the sites of subcutaneous injections of drug solutions was studied [54]. The results showed that drug solutions with pH 7.0 or in the pH range of 5.0 - 8.5 and those with hypotonic or isotonic activity did not cause local hyperthermia, post-injection necroses and abscesses. At the same time, the same drug solutions, but with greater acidic activity (with pH value less than 4.0) and/or with greater osmotic activity (with osmotic activity more than 600 mosmol/L water), caused the formation of a nidus in the skin at the injection site, aseptic inflammation of the subcutaneous fatty tissue, infiltrate and necrosis. In this regard, infrared monitoring of the dynamics of local

skin temperature in the place of drug injection was proposed to assess the post-injection safety of drug solutions (RU Patent No 2304769; RU Patent No 2396562).

Following this, it was reported that if the process of drug injection is supplemented by infrared monitoring of the dynamics of local skin temperature at the injection site, it is possible not only to detect local hyperthermia and the process of postinjection inflammation, but also to prevent postinjection necrosis and abscess. It was found that for this purpose, if local hyperthermia appears after injection, it is necessary to inject 0.25% novocaine urgently (within 5 minutes after injection). The volume of the novocaine solution should ensure effective dilution of the hypertonic solution of the aggressive drug. This method has been shown to provide timely normalization of the osmotic and acidic activity of the drug solution inside the tissues, so it preserves the reversible nature of aseptic inflammation and prevents necrosis. Increasing the time period between the injection and pricking of the drug infiltrate with hypotonic novocaine solution for more than 5 minutes reduces the effectiveness of the method to zero [48].

However, these reports went unnoticed by most researchers around the world. Therefore, up to now, most researchers do not question the quality of drug solutions ready for injection, do not consider their acid and osmotic activity, and do not suspect their physical and chemical aggressiveness and local irritation to the tissues at the injection sites. In all likelihood, this also explains why infrared monitoring has not been included in the accepted medical standard for injections to date, and the pre-dilution of highly concentrated drug solutions with water for injection is not included in the medical standard for the prevention of iatrogenic postinjection disease, known as Nicolau syndrome.

#### 4. Discussion

Due to the study of the influence of the physical and chemical properties of drug solutions on their local effect during injections, it was found that **early** mechanism of local drug action in the injection site has a nonspecific nature. Most often, the nonspecific effect of drug solutions is due to their acidic and hypertonic activity [5,6]. It turned out that drug solutions ready for injection and considered of high quality today may not have a pH of 7.4 and an osmotic activity of 280 - 300 mosmol/L water [26-29, 54]. Moreover, studies have shown that most modern drug solutions ready for injection have a pH of less than 7.0. Therefore, most drug solutions are acidic solutions. Because of this, most drug solutions have a local irritant effect as acids at injection sites. In addition, it has been shown that all drugs have osmotic activity., **The** value of which increases with increasing concentration of dissolved ingredients [26]. It has been reported that since some drug solutions have a high total concentration of dissolved ingredients, they are hypertonic solutions and that is why they can dehydrate tissue cells at injection sites and have a local irritant effect [29, 53,54].

It is reported that the osmotic activity of drug solutions is currently not controlled. The consequence of this is that drug solutions that are considered quality today can have any osmotic activity (i.e., drugs can be hypotonic, isotonic, or hypertonic) [26-29]. Therefore the value of the osmotic activity of drug solutions remains unknown to consumers. At the same time, it is reported that drug solutions that have a total concentration of dissolved ingredients greater than 5% have hypertonic activity, but post-injection necroses and abscesses are most often caused by solutions that have a value of total concentration greater than 10% [53]. It has been shown that excessively strong local acidifying and/or dehydrating effects of drug solutions may underlie their local irritating effects, which may sometimes be excessively strong or prolonged, so can be

transformed into a cauterizing effect. Therefore, injections of drugs with excessive local irritant effects can cause postinjection aseptic inflammation, necrosis and abscess [26,29,53].

Based on the fact that the assessment of the local irritant effect of drug solutions during injection is not yet included in the standard for evaluating the quality of drugs, it was proposed to monitor the safety of injections using a thermal imager. It was shown that the appearance of a focus of local hyperthermia in the skin at the injection site indicates the development of local inflammation. It is reported that immediate injection of 0.25% novocaine solution or water into the drug infiltrate excludes subsequent necrosis and abscess, if this method is used no later than 5 minutes after injection and the solution is injected in a volume that provides effective dilution of aggressive medication several times up to deprivation of hypertonic activity [48,54].

## 5. Conclusion

In recent years, there are more and more reports that the cause of local postinjection complications, including Nicolau syndrome, is excessive local irritant effect of drugs due to high acidity and hypertonic activity. Analysis of the current drug quality control standard showed that it does not include an assessment of the magnitude of the osmotic activity of drugs and the strength of their local irritant effect on the tissues at the injection sites.

These data suggest that many drugs, including antiseptics, local anesthetics, nonsteroidal anti-inflammatory drugs, steroids, radiocontrast drugs, antibiotics, anticoagulants and many other drugs can have a local irritant effect in the first few minutes after injection due to their excessive osmotic activity, which can have a strong dehydrating and local irritating effect on tissue cells at the injection site. In these circumstances, to improve the safety of the injection it is necessary to carefully study the Pharmacopoeia requirements for the quality of the selected drug, clarify the manufacturer and batch number of the drug. After that, it will be possible to study the contents of the Technical Passport of the drug, which was issued for a specific batch of the drug by the technical control department or the control laboratory of the pharmaceutical company. These documents contain information about the exact formulation and physical-chemical quality parameters of the drug, including the indicator of its acidity (alkalinity) with the exact indication of the pH value of the drug solution in this batch. But it must be remembered that these documents do not contain information about the osmotic activity of the drug solution. At the same time, the value of the osmotic activity of the drug can be measured in a biochemical laboratory using an osmometer. The information received about the pH and osmotic activity of the medicinal solution indicate whether it should be diluted with 0.25% novocaine or water before injection and how many times it should be diluted. It is also reported that infrared monitoring of the dynamics of local skin temperature at the injection site can provide additional monitoring of postinjection drug safety.

Consequently, the accumulated data confirm that excessively high concentration of dissolved ingredients gives drug solutions excessively high hypertonic activity, which in injections can cause excessive dehydrating effect on tissue cells, local irritating action, aseptic inflammation of necrosis and abscess. In this regard, there is hope that consideration of osmotic activity, acid activity, local irritating effect of drug solutions during injections and the use of thermal imaging to record the dynamics of local skin temperature at the injection site will reduce the likelihood of local postinjection complications and Nicolae syndrome during injections of modern drugs. In addition, there is every reason to include the assessment of the osmotic activity of drug solutions and their local irritant effect on tissues during injections into the existing standard of quality control of drugs.

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## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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