Received: 30 July 2020 | Accepted: 30 November 2020

DOI: 10.1111/jocd.13888

REVIEW ARTICLES

JCD Journal of Cosmetic Dermatology WILEY

Microneedle systems as medical devices for esthetical treatments: A risk assessment approach

Luis Alberto del Rio PharmD, PhD[1] | David Baeza PharmD, PhD[2] | Nuria Salazar PharmD, PhD[1]

[1]Pharmacy and Pharmaceutical Technology Department, Faculty of Pharmacy, University San Pablo CEU, Madrid, Spain

[2]Chemistry and Biochemistry Department, Faculty of Pharmacy, University San Pablo CEU, Madrid, Spain

Correspondence
Luis Alberto del Rio, Faculty of Pharmacy, University San Pablo CEU, Urbanización Montepríncipe, 28760 Boadilla del Monte, Madrid, Spain.
Email: delrio@ceu.es

Abstract

Background: Microneedling devices are being used as a surgical technique without a clear regulatory category. They can become dangerous considering that these kind of devices can easily be bought and used by nonqualified people.

Aims: Our aim has been to demonstrate that microneedling devices used in dermatological surgery are Medical Devices according to the current regulations.

Patients/Methods: After a thorough review in the European Union and USA medical device classification, we consider microneedling systems as Class II (US) or IIa (EU).

Results: Therefore, they must follow the regulations established for medical devices. A risk assessment has also been made, in which the technical and scientific deficiencies in their design and manufacturing have been recognized in addition to including compulsory information for the regulatory agencies and most importantly for the final user.

Conclusion: It can be concluded that microneedling is an interesting tool in dermatology although more information related to its safety needs to be submitted. In addition, its use by nonprofessional people does not guarantee the safety of the user.

KEYWORDS

microneedling devices, regulatory affairs, risk factor, safety

1 | INTRODUCTION

Microneedling is an invasive process that involves repeated skin perforation with microneedling devices (MND) with the intention of modifying the skin structure in order to achieve a pharmaceutical or dermatological objective. This technique is originated from an American patent in the early 1970's with an exclusive application for pharmaceutical drug delivery through the skin.[1] Nowadays there are many scientific publications enabling the transdermal passage of drugs to the circulation system.[2]

In 1995, Orentreich and Orentreich [3] described a dermal puncture technique used to remove scars employing a tri-bevel hypodermic needle that was inserted and maneuvered to make subcuticular cuts which were then repaired by the formation of connective tissue during the healing process. Afterward, Fernandes [4] developed another therapy called percutaneous collagen induction consisting of the perforation of the stratum corneum using a special device with the purpose of treating scars that result in microchannels with variable length and produce a mild inflammatory response, when combined with other treatments such as autologous platelet-rich plasma, chemical peels, filler injections, or laser treatment, a greater improvement was reported.[5] Hou et al have asserted microneedling seems to be safe and effective although more randomized controlled trials are needed.[6]

Microneedles are assembled in devices, a typical one can be seen in Figure 1, with a handle attached to a roller or stamp plate (which can be electrically assisted). The device contains a variable number of needles (up to several hundreds) made of steel that is rolled directly

over the skin. The needles can have different geometries and shapes, whose application repeatedly on the skin can result, depending on use, in dozens of holes per cm^2 with a highly variable depth.[7]

This micropunction technique has been marketed by trademarks such as Dermaroller® (Dermaroller GmbH, Wolfenbüttel, Germany) which is recommended [8] for both healthcare professionals and the general public. At the same time, a panoply of counterfeit or pseudo-legal products are appearing on Internet service platforms with affordable prices but which are probably harmful.[9]

This work aims to outline that MND belong to the Medical Device Category following current regulation and define the main critical requirements to facilitate their risk assessment.

2 | REGULATORY SITUATION OF MICRONEEDLE SYSTEMS

2.1 | Microneedle systems as medical devices

Medical devices are controlled products that are directly related to patients' health and lives; consequently, it is important to specify whether the MND characteristics fit into those of a regulated medical device. For this, the legal definition of a medical device is required, either through Section 201(h) FD&C Act [10] or by that stated in European Regulation 2017/745,[11] both of which are very similar, as they refer to any apparatus or other article that is intended, among other functions, to affect the structure or any function of the body (FDA regulation) or replace or modify the anatomy or a physiological or pathological process or state (European Union Regulation). Therefore, it can be affirmed that MND come under the definition of a medical device as they are intended to modify the structure of the human body, as they clearly penetrate the stratum corneum [12] provoking platelet-derived and fibroblast growth factor release and neovascularization in the papillary dermis.[13] Furthermore, Alster et al in a complete review [14] are of the opinion that scars or striae can be treated with needle depths from 1.5 to 3.0 mm, which is clearly invasive, and they also recommend pinpoint bleeding as the treatment endpoint.

FIGURE 1 Typical roller micropunction device

2.2 | Legal classification

Once MND have been defined as medical devices, they can be classified following the four classes established by the European Union (EU): Classes I, IIa, IIb, and III (low-risk, low-medium risk, medium-high risk, and high risk, respectively) and the three classes set by the FDA which include Classes I (low risk), II (which corresponds to European sub-classes IIa and IIb, as moderate risk), and III (significant risk).

It is important to properly define which class MND belong to because it has implications in their safety and commercialization requirements. For a Class I medical device, in the United States, only a premarketing notification without needing a clinical trial is required, while in EU, it is enough to "make a self-declaration" that the manufacturers meet the essential requirements of the national competent authority in the country of origin.[15] For instance, dermabrasion devices such as brushes, scrapers, and blades by the mechanism of wearing away and removal of layers of the skin by shear force are considered as Class I medical devices. In the case of Class II medical devices, it is generally necessary in US as well as in EU regulation to present a clinical trial that demonstrates their safety, as well as evidence data confirming that the device works as expected.

All marketed Class II and III medical devices and those of Class I that have sterility specifications, with a measurement function or reusable surgical instruments must be registered by a regulatory agency from any of the Member States in the EU and must bear the *Conformité Européenne* brand (CE) which verifies that they follow the established directives for medical devices and allows them to circulate freely in the EU market. At the same time, the participation of a Notified Body (NB), with its corresponding registration number included in the product labeling, is required. The NB must evaluate the compliance with the essential requirements for medical devices, including clinical data and must perform audits on the manufacturers in order to verify their quality assurance system, their operating license, the existence of a qualified technical manager, the quality of facilities, and the qualifications of the personnel.

To classify MND in accordance with EU regulation, their main characteristics are submitted to the 22 classification rules from Regulation (EU) 2017/745 (Annex VIII) according to their intended purpose, duration of use, and invasiveness which go from least to greatest risk. After the application of the abovementioned rules to a MND prototype, as can be seen in Table 1, MND are considered to be invasive products as the 1st, 2nd, 3rd, and 4th rules do not apply for them. From the 5th rule on, medical devices are considered as invasive. MND do not conform to the 5th rule as they are not intended to be used through a body orifice so it should be assumed that MND are Class IIa medical devices as the 6th rule applies due to their transient use (less than 60 minutes) which is presumed for these types of devices. Rule 7 does not apply to MND as it does not correspond to short-term duration (60 minutes-30 days) nor do any of the subsequent rules.

To classify MND according to the American regulation, the FDA released a draft guidance on MND [16] where it is claimed that as MND can penetrate beyond the stratum corneum in living layers of

TABLE 1 Application of Medical devices classification rules (EU Regulation) to the Microneedling devices

Rules	Class. Comments
1st	Noninvasive, Class I. Default
2nd	Noninvasive, Class I. Except devices intended for channeling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body whereas Classes IIa, IIb, and III are applied
3rd	Noninvasive, Class I. Except devices intended for modifying the biological or chemical composition of human tissues or cells, blood, or devices to be used in vitro in direct contact with human cells, tissues or organs taken from the human, whereas Classes IIa, IIb, and III are applied
4th	Noninvasive, Class I. Except Devices which come into contact with injured skin or mucous membrane if they are not used as a mechanical barrier whereas Classes IIa and IIb are applied
5th	Invasive device with respect to body orifices. Depending on its duration use, they could be classified as Class I, IIa, or IIb
6th	Invasive device. Surgically invasive devices intended for transient use are classified as class IIa. With many exceptions which do not apply to MND
7th	Invasive device. Surgical invasive devices intended for short-term use are classified as class IIa

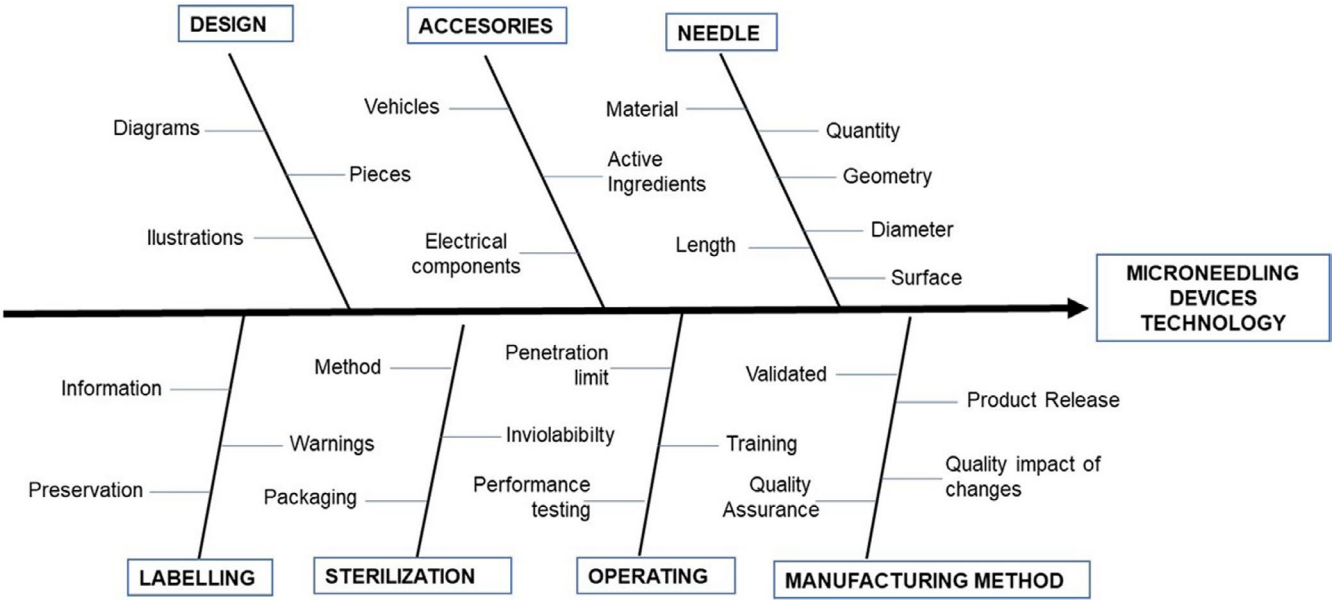

FIGURE 2 Ishikawa diagram on the issues considered in Microneedling devices safety

the skin, they are devices with greater risk; therefore, they exceed the Class I legal restriction, which supports our proposal for a Class II (IIa EU) classification of MND.

The FDA in its postmarket surveillance, alerts, and withdrawals work required a US company to withdraw its MND [17] because they stated that they manufactured Class I medical devices on its labels and promotional materials but it turned out to be microneedling with indications such as *"It produces micro-injuries to the skin in order to aid in the production of collagen and elastin."* Another case was that of an electrical micropunction product based on 11 disposable needles. In its promotional materials, the manufacturer claimed that: "*controlled micro-injuries to the skin were created in order to stimulated collagen and elastin production*" which motivated an FDA warning letter followed by a product recall.[18]

Additionally, EU Regulation 2017/745 considers, in Article 1, paragraph 2 the consideration of a group of products without an intended medical purpose which are listed in Annex XVI. MND could be considered, as referred to in point 2, as "*Products intended to be totally or partially introduced into the human body through surgically invasive means for the purpose of modifying the anatomy or fixation of body parts with the exception of tattooing products and piercings.*" These groups of products claimed an esthetic or another nonmedical purpose, but they are similar to medical devices in terms of working and risk profile so they should be covered by this Regulation, until future Regulations that establish their specifications have been be developed. Nowadays, according to the FDA Regulation, MND do not fall within any classification and there is no legally marketed predicate device upon which to base a determination of substantial equivalence. However, the FDA has established, under section 513(f)[2] of the FD&C Act, a pathway for low-moderate risk devices classification to class I or class II, which do not have a legally marketed predicate, referred to as the De Novo classification process.

TABLE 2 Risks to be consider in the Microneedling devices regulatory process

Items	Risks	Failure mode effects
Mode of use	Punctures, frequency, depth and endpoint Part of the body User´s skin type Cleanliness and disinfection requirements	Aggressive punction Mucous membrane closeness Thickness, dehydration Reuse, contamination, illnesses transmission
Indications of use	Scars, burns, wrinkles and depth of facial lines, cellulite and stretch marks, dermatosis, acne, alopecia, collagen production, angiogenesis	Skin, mucous membranes, wounds, nerves, tissues and vascular system contact. Limited evidences about their short- and long-term use
Biological interaction	Biocompatibility In vitro-in vivo reactivity	Toxicity Extractives
Contraindications	Wound presence Medication concomitant use (anticoagulant, immunosuppressant, etc) Use of cosmetic products Esthetic treatments (eg, laser, chemical peeling, and tanning)	Infections Bleeding, infections Toxicity (ingredients) Hyper reaction, hyper pigmentation

Once a De Novo request is granted for a particular MND, it should be classified as a medical device, class I or II, and can be marketed and serve as a predicate for future device approvals.[19]

3 | RISK ASSESSMENT APPROACH FOR MICRONEEDLING DEVICES

In this work, we carry out a Risk Assessment Analysis, for which three different points of view are considered: the manufacturer´s view relating to the medical device design and manufacturing process, the benefit-risk balance and finally the usage by the end user.

A systematic approach to risks management during the process will lead to the development of quality and reliable medical devices.

3.1 | Design and manufacturing risk assessment

Referring to MND risks that could arise during that first stage, it is necessary to confirm that it works properly, for that the manufacturer must establish systems and processes in order to identify trends, patterns, or signals that may reveal new risks or safety concerns. An Ishikawa diagram in Figure 2 compiles the issues which must be considered to ensure its safety such as its design, the needle characteristics, its accessories, manufacturing method, sterilization requirements, and labeling information.

3.2 | Risk—Benefit balance assessment

Manufacturers must demonstrate to the regulators the compliance of their medical devices. For that it is necessary, that regulators set the common specifications regarding risk management and clinical evaluation which ensure the safety and efficacy of the device. It should be mentioned that the literature previously cited has important deficiencies regarding these kinds of medical devices in the effect of their long-term use, the part of the body where they are applied and the specific biological risks associated with MND use. Furthermore, in normal conditions of use, several conditions must be included, among them, nerve and vessel injury, infection transmission between users, skin reactions that would result in scar formation, hyperpigmentation, skin inflammation, tattoo ink reaction and even the use of the device when it comes into contact with other materials and substances. We are aware that MND are being used in practice alone or combined such as with radiofrequency [20] to facilitate the passage through the skin of products such as creams, gels,

TABLE 3 Risk level classification of failures

Severity (S)	Frequency (F)	Detectability (D)	Risk priority number
1. Insignificant—Transitory discomfort	1. Unappreciable. Never happened, unlikely to occur.	1. Immediately	RPN = S x F x D Acceptable < 12 Serious: 13 - 47 Unacceptable > 48
2. Minor—Nonmedical intervention is required	2. Rare. Observed < 10%	2. High	
3. Serious—Medical intervention is required	3. Sometimes. Observed 10%-30%	3. Appreciable during its use	
4. Critical—Permanent damage	4. Frequently. Observed 30-70%	4. Low	
5. Catastrophic—Death	5. Always. Observed > 70%	5. Undetectable	

TABLE 4 Failure Mode Effect Analysis for Microneedling devices users

Process	Failure Mode	Frequency (F)	Severity (G)	Detectability (D)	Risk Priority Number (RPN)
System and its components failure	Physical danger (eg, blunt)	2	3	3	18
	Mechanical danger (eg, impact, motorized components)	2	2	3	12
		1	3	3	9
	Electrical risks (eg, electrical safety)	1	3	5	15
	Chemical risks (eg, residues)	4	4	5	80
	Biological risks (eg, contamination)	3	2	2	12
Users Characteristics	Without physical abilities	2	2	5	20
	Limited sensorial abilities	1	3	5	15
	Limited cognitive abilities	4	3	4	48
	Associated illnesses	2	2	5	20
	Alterated emotional state	5	3	3	45
	Low sanitary education	1	1	1	1
	Used by clinical professional	3	2	3	12
Given information	Lack of diagrams	3	3	3	18
	Not clear or not enough instructions				

and solutions with cosmetic purposes or even containing a panoply of medicines (eg, lidocaine, tacrolimus, vitamins, anti-cellulite active products, glycolic acid, hyaluronic acid, latanoprost, hydrocortisone, and plasma) In this case, it should be confirmed that the products applied are manufactured under the requirements for injectable products and meet parenteral specifications to guarantee their safety as they are going to pass through the skin. The main requirements to ensure MND safety, taking into account both the European Union Regulation for medical devices [11] and the US Biological evaluation Guidance,[21] are summarized in Table 2. There we have combined them with their failure mode effects. This approach could be used by the manufacturers to assess the device risk analysis as well as by the regulators to verify MND safety.

3.3 | User risk assessment

The third approach that is recommended is to evaluate the MND risks under different use scenarios, considering dangers associated with the device or its accessories case of failure and circumstances which are unable to make the use of the device by the user safe and effective.[22] The manufacturer must provide enough information regarding the patient´s safety (warnings, precautions, contraindications, etc) by considering factors such as technical knowledge, experience, education, training, environmental conditions of use and even the abilities of nonprofessional users.

A Failure Mode and Effects Analysis, FMEA, [23] has been used to allow us to collect all the possible failures that can have direct repercussion on patient´s safety. As can be seen in Table 3, different scenarios have been considered, each being assigned a mark between 1 and 5 points according to its Severity, Frequency, and Detectability. Once each parameter has its correspondent mark, the Risk Priority Number (RPN) can be calculated by multiplying them and the risks classified as acceptable, serious, and unacceptable.

Once the Severity, Frequency, and Detectability values are defined from low to high risk in Table 4, different potential harms for each possible use are described. From the possible failures detected, the lack of hygiene practices and the presence of associated illnesses are considered as unacceptable, although they can be mitigated if MND are used in medical practice by professionals. The risks identified as serious represent more than 50% of the total.

4 | DISCUSSION

The microneedling technique is used by medical professionals in their surgery practices, but it should be taken into account that medical devices are also being used by estheticians, and even by consumers themselves at home, so proper regulation for MND is needed in order to ensure patient safety. After the evaluation of the available information related to its safety, technical requirements, and indications of use, we consider that MND are as yet not properly regulated. As MND characteristics fit completely under those of Medical Devices, such as invasive surgery-type devices, they must be deemed as medical device Class II- IIa (FDA-EU) until the proper medical devices without an intended medical purpose regulation are developed.

However, more scientific studies indicated by the associated risks such as infections, skin inflammation, illnesses, and concomitant treatments, among others are necessary. From the Failure Mode and Effects Analysis, some recommendations to be considered by the manufacturers should include safety aspects in MND design, manufacture, and quality assurance which could facilitate MND risk-benefit balance. The risk assessment identifies the hazards as acceptable, serious, and negligible based on their criticality. If one risk is classified as unacceptable, it could be mitigated partially or completely when MND are used by medical professionals but it could not be guaranteed when they are used by nonprofessional users.

This work offers a guide to be used both by the manufactures to facilitate MND Risk assessment performance and by the authorities who must guarantee the quality, safety, and efficacy of medical devices.

ACKNOWLEDGMENTS

The authors thank Brian Crilly for his English language editing.

AUTHOR CONTRIBUTIONS

Luis Alberto del Rio involved in methodology, investigation, writing-original draft, and visualization. David Baeza involved in conceptualization, methodology, and review and editing. Nuria Salazar involved in methodology, investigation, writing-review and editing, and visualization. All authors approved the final version of the article for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Luis Alberto del Rio https://orcid.org/0000-0002-7329-4893

REFERENCES

1. Gerstel MS.Place VA inventors; Alza Corporation., assignee. Drug Delivery Device. United States patent US 3,964,482. 1976 Jun 22.
2. Burton SA, Ng CY, Simmers R, et al. Rapid intradermal delivery of liquid formulations using a hollow microstructured array. *Pharm Res*. 2011;28:31-40.
3. Orentreich DS, Orentreich N. Subcutaneous incisionless (subcision) surgery for the correction of depressed scars and wrinkles. *Dermatol Surg*. 1995;21:543-549.
4. Fernandes D. Percutaneous collagen induction: an alternative to laser resurfacing. *Anaesthetic Surg J*. 2002;22:307-309.
5. Villani A, Annunziata MC, Luciano MA, Fabbrocini G. Skin needling for the treatment of acne scarring: A comprehensive review. *J Cosmet Dermatol*. 2020;00:1-8. https://doi.org/10.1111/jocd.13577
6. Hou A, Cohen B, Haimovic A, et al. Microneedling A Comprehensive Review. *Dermatol Surg*. 2017;43:321-339.
7. McCrudden MT, McAlister E, Courtenay AJ, et al. Microneedle applications in improving skin appearance. *Exp Dermatol*. 2015;24:561-566.
8. Dermaroller GmbH. Germany. Medical Care. 2020 [cited 2020 Jun 23]; [about 2 screens]. Available from: https://www.original-dermaroller.de/en/medical-care
9. Abraham A. Chinese women warned over 'potentially lethal' microneedle roller after beauty treatment takes Hong Kong by storm. Daily Mail Online. 2011 August 17 [cited 2020 Jun 1]; [about 2 screens]. Available from: http://www.dailymail.co.uk/femail/article-2026700/Microneedle-Therapy-System-potentially-lethal-Chinese-women-warned.html
10. Food and Drug Administration, Center for Devices and Radiological Health, USA. How to Determine if Your Product is a Medical Device. [cited 2020 May 1]; Available from: https://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/ucm051512.htm
11. The European Parliament and The Council. Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. 2017 April 5. [cited 2020 May 1].
12. Sasaki GH. Micro-needling depth penetration, presence of pigment particles, and fluorescein-stained platelets: clinical usage for aesthetic concerns. *Aesthet Surg J*. 2016;37:71-83.
13. Aust MC, Reimers K, Kaplan HM, et al. Percutaneous collagen induction-regeneration in place of cicatrisation? *J Plast Reconstr Aesthet Surg*. 2011;64:97-107.
14. Alster T, Graham P. Microneedling A Review and Practical Guide. *Dermatol Surg*. 2018;44:397-404.
15. Global Legal Research Center. Approval of Medical Devices. USA. The Law Library of Congress. September 2014. [cited 2020 Mar 13]; Available from: https://www.loc.gov/law/help/medical-devices/approval-of-medical-devices.pdf
16. Food and Drug Administration, Center for Devices and Radiological Health, USA.Regulatory Considerations for Microneedling Devices. Draft Guidance for Industry and Food and Drug Administration Staff. September 15, 2017.
17. Food and Drug Administration, Compliance Actions and Activities, USA. Derma Pen, LLC 1/9/15 FDA Warning Letter January 09, 2015. [cited 2020 Jan 20];. Available from: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm429899.htm
18. Food and Drug Administration, Compliance Actions and Activities, USA. Eclipse Aesthetics LLC 3/28/16 FDA Warning Letter. March 28, 2016. [cited 2020 Feb 22]; Available from: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm500631.htm
19. Food and Drug Administration, Center for Devices and Radiological Health, USA. Evaluation of Automatic Class III Designation (De Novo) Summaries. [cited 2020 Apr 13]; Available from: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm
20. Zahr AS, Kononov T, Sensing W, Biron JA, Gold MH. An open-label, single-site study to evaluate the tolerability, safety, and efficacy of using a novel facial moisturizer for preparation and accelerated healing pre and post a single full-face radiofrequency microneedling treatment. *J Cosmet Dermatol*. 2019;18(1):94-106.
21. Food and Drug Administration, Center for Devices and Radiological Health, USA. Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. [cited 2020 May 15]; Available from: https://www.fda.gov/media/85865/download
22. Food and Drug Administration, Center for Devices and Radiological Health, USA. Applying Human Factors and Usability Engineering to Medical Devices. 2016 Feb. [cited 2020 May 3]; Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices
23. Lin QL, Wang DJ, Lin WG, et al. Human reliability assessment for medical devices based on failure mode and effect analysis and fuzzy linguistic theory. *Safety Sci*. 2014;62:248-256.

How to cite this article: del Rio LA, Baeza D, Salazar N. Microneedle systems as medical devices for esthetical treatments: A risk assessment approach. *J Cosmet Dermatol*. 2021;20:2052–2057. https://doi.org/10.1111/jocd.13888