DE NOVO CLASSIFICATION REQUEST FOR SKINPEN PRECISION SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Microneedling device for aesthetic use.** A microneedling device for aesthetic use is a device using one or more needles to mechanically puncture and injure skin tissue for aesthetic use. This classification does not include devices intended for transdermal delivery of topical products such as cosmetics, drugs, or biologics.

NEW REGULATION NUMBER: 21 CFR 878.4430

CLASSIFICATION: II

PRODUCT CODE: QAI

BACKGROUND

DEVICE NAME: SkinPen Precision System

SUBMISSION NUMBER: DEN160029

DATE DE NOVO RECEIVED: July 5, 2016

CONTACT: Bellus Medical, LLC
4505 Excel Parkway
Suite 100
Addison, Texas 75001

INDICATIONS FOR USE

> SkinPen® Precision System is a microneedling device and accessories intended to be used as a treatment to improve the appearance of facial acne scars in adults aged 22 years or older.

LIMITATIONS

The sale, distribution, and use of the SkinPen Precision System is restricted to prescription use in accordance with 21 CFR 801.109.

This product is not intended for transdermal (under the skin) delivery of topical products such as cosmetics, drugs, or biologics.

Safety and effectiveness for needle depth settings greater than 1.5 mm has not been evaluated.

The SkinPen Precision System allows for incremental increase in settings of up to 2.5 mm to allow for the variability in thickness of healthy skin and acne scar tissue. However, the device has not been clinically evaluated at cartridge settings of greater than 1.5 mm. As there are fine structures (*i.e.*, nerve branches and accompanying blood vessels) that run under the skin and are essential to proper tissue function, it is not recommended to treat at needle depths greater than 1.5mm. It is essential that the thickness of the patient's skin in each anatomical area to be treated is assessed by a qualified clinician to address any potential risk of injuring these structures. Such structures include (but are not limited to) the supraorbital nerve (the terminal branch of the frontal nerve that provides the sensory innervations for the skin of the forehead, mucosa of frontal sinus, and the skin of the upper eyelid) and the temporal, buccal and marginal mandibular branches of the facial nerve (motor nerve that controls facial muscle movement). No adverse events were observed relating to such structures in the SkinPen Precision System clinical study when treating at needle depth of up to 1.5 mm. Please refer to Bellus provided training module on superficial nerve and vessel facial anatomy for additional information.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The SkinPen® Precision System consists of a microneedling pen handpiece (SkinPen Precision) and a sterile needle cartridge (SkinPen Precision Cartridge). The accessories are a charging base and a BioSheath. A SkinPen Precision System treatment kit is provided separately and contains the following:

- SkinPen Precision Cartridge: sterile, disposable needle cartridge. Not to be resterilized or reused.
- SkinPen BioSheath: nonsterile, disposable cover for the microneedling pen handpiece to avoid contamination of the SkinPen Precision
- Lift HG: hydrogel wound dressing (without drugs and/or biologics) to protect against abrasion and friction during the microneedling procedure. May be applied to prevent skin from drying out post procedure

Table 1: SkinFuse Lift HG Regulatory Information

Device Trade/Proprietary Name	SkinFuse Lift HG
Device Common Name	Hydrogel wound dressing without drugs and/or a biologic
Device Class	Class I, 510(k) Exempt
Classification Regulation	878.4022
Product Code	NAE

Table 2: Device Characteristics:

Control mechanism	Microprocessor – Embedded Software Controlled
Operating principle	Rotary
Energy type	Charging base: AC powered SkinPen Precision microneedling pen handpiece: rechargeable Li+ batteries
Materials	BioSheath: (b) (4) SkinPen Precision cartridge (needle): stainless steel (b) (4) SkinPen Precision cartridge (cartridge): (b) (4)
Performance Specifications	
Motor	Designed to operate continuously at constant speed
Motor speed	1 speed: 7000 RPMs (6300-7700 RPMs)
Needle penetration depth	11 depth settings from 0 mm to 2.5 mm in 0.25 mm increments. Safety and effectiveness for settings greater than 1.5 mm has not been evaluated.
Number of needles	14
Shelf-life/reliability	SkinPen Precision microneedling pen handpiece: ≥ 2000 hours of use SkinPen Precision cartridge: (b) (4)
Reprocessing/Cross-Contamination	
Re-Use Protection	The SkinPen Precision cartridge has a lock-out feature that prevents the installation of a used disposable cartridge for the second time
Fluid Ingress Protection	Sealed SkinPen Precision cartridge to prevent fluid intake from patient to the device
Sterility	SkinPen Precision cartridge: provided sterile (EO) SkinPen Precision System: not sterile
Packaging	Sterile, disposable SkinPen Precision cartridge packaged and labeled individually. Proprietary SkinPen Precision cartridge.
Handpiece cover	During use, the SkinPen Precision microneedling pen handpiece is covered with a single use barrier sleeve (BioSheath). The sleeve is not sterile.
Non-sterile reprocessing	The SkinPen Precision microneedling pen handpiece is reusable and is provided non-sterile. For reprocessing, use with BioSheath and clean/disinfect with a Sani-Cloth HB® germicidal disposable wipe.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The patient contacting components of the device are the needle cartridge and the SkinFuse Lift HG hydrogel. Both components have contact with breached/compromised skin for a limited duration (< 24 hours). Testing was provided on the final, finished device including evaluation of cytotoxicity, irritation, and sensitization per the FDA guidance document "*Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.*"

SHELF LIFE/STERILITY

The needle cartridge is a sterile, single use component of the device system. The cartridge is sterilized using EO sterilization and sterilant residuals were quantified and under the acceptable limits for EO and ECH. The sterilization method was validated per ISO 11135-1:2007 (*Sterilization of health care products -- Ethylene oxide -- Part 1: "Requirements for development, validation and routine control of a sterilization process for medical devices"*) using the overkill half cycle method. The SAL for the needle cartridge is 10^{-6}.

The shelf-life of the needle cartridge was evaluated after accelerated aging equivalent to (b) (4) The cartridge was evaluated using the peel strength test, dye penetration testing, and burst testing. The test article met the acceptance criteria for each test.

SkinPen Precision cartridge functional testing after aging: To evaluate the ability of the cartridge to continue to meet performance specifications at the end of the intended shelf-life, cartridges which had aged beyond the expiration date (b) (4) were subjected to a series of functional tests. These tests included evaluation of the depth setting indicator, retraction verification, needle adjustment, and lock spring mechanism engagement. All 10 cartridges met the acceptance criteria for the tests demonstrating maintenance of performance characteristics over the labeled shelf-life.

REPROCESSING/CROSS-CONTAMINATION

The handpiece is a reusable component of the device system intended to be used on multiple patients. To mitigate the risk of cross contamination, three reprocessing tests were completed. First, the ability of the BioSheath to maintain an effective barrier to test soil was evaluated. Motile species of bacteria were introduced to areas of the sheath which were considered to be most susceptible to penetration, such as the seam. Four test organisms were used. Results show that no test organisms could be recovered from the handpiece.

Second, the cleaning and disinfection instructions were validated. The validation testing was completed using the instructions from the labeling and a test soil consisting of four different test organisms. The device was soiled under conditions representative of a

clinically relevant worst case. After soiling, the device was cleaned according to the instructions in the user manual. Several areas on the reusable component of the device were identified as difficult to clean. These areas were sampled to confirm that the cleaning procedure had adequately disinfected even the most challenging areas of the device. Results support that the cleaning instructions included in the device labeling are acceptable.

Finally, fluid ingress testing was completed. In addition to soiling that may occur on the outside of the reusable component during use, there is a risk that contaminants including blood and tissue that are generated during the treatment procedure may ingress through the needle cartridge and into the handpiece. Testing was completed under conditions representative of a clinically relevant worst case, using a test fluid consisting of four test organisms. Following simulated use, no organisms were detected beyond the cartridge barrier.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The following Electrical Safety and EMC testing has been performed:

- IEC 60601-1: 2005 (3rd Edition) +CORR.1:2006+CORR.2:2007A1:2012 or IEC 60601-1:2012 reprint, General safety standard: safety requirements for medical electrical systems
- IEC 60601-1-2: 2014 (Edition 4), Medical electrical equipment Part 1-2 - General
- requirements for basic safety and essential performance – Electromagnetic compatibility.
- IEC 60601-1-6: Collateral Standard: Usability
- IEC 62366 – Application of Usability Engineering to Medical Devices

The SkinPen Precision System passed all relevant portions of the testing.

SOFTWARE

All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy. The agency considers the software to be a moderate level of concern (LOC) because inadvertent software errors could result in skin injury to the patient.

All of the elements of software information corresponding to moderate LOC devices as outlined in FDA's guidance document *"Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"* (issued May 11, 2005) were provided. Adequate documentation describing the software development program was provided. Verification and validation (V&V) activities were described at the unit, integration, and system level and the results of these activities met the pass/fail criteria. In addition, a hazard analysis from both the patient's and user's standpoint was performed, hazards were addressed; and an appropriate validation process has been carried out.

Overall, the software documentation included in the De Novo request is in sufficient detail to provide reasonable assurance that the software will operate in a manner described in the specifications.

PERFORMANCE TESTING - BENCH

Bench testing was conducted to demonstrate that the SkinPen Precision System performs as expected under the anticipated conditions of use. This testing included evaluation of key device parameters such as needle penetration depth, puncture rate, and the ability of the safety features of the device to mitigate the risk of cross-contamination. The following bench testing was conducted to demonstrate the device performance characteristics:

- Puncture rate: The device was tested to ensure that the motor could achieve the intended puncture rate within the pre-established tolerance (7000 RPM ± 10%) over the intended operating time. The purpose of the test was to demonstrate that the motor speed provides assurance for consistent speed, mitigating the risk of mechanical injury.
- Needle deformation durability: The device was tested using (b) (4) to demonstrate that the needles in the SkinPen Precision cartridge can withstand continuous use in extreme conditions. The skin substitutes produced (b) (4) resistance, which are (b) (4) Results showed minimal needle deformation (b) (4). Therefore, the exposed portions of the needles can withstand extreme treatment conditions and continue to perform as intended.
- Retraction verification: The device was tested to demonstrate that when the SkinPen Precision cartridge is in the "home" position, the needles are retracted within the cartridge housing. The device met the visual inspection acceptance criteria, demonstrating that the use of the "home" position helps to mitigate the risk of needle stick injuries.
- Reciprocating motion and needle extension accuracy: Testing was conducted to demonstrate that at the extreme parameters of device use the needle extension does not go beyond what has been demonstrated to be safe in the clinical literature. A summary of the clinical literature provided in the submission to support the depth is included in the section below. The device was tested at the highest parameter for needle depth, 2.5 mm, and was considered to have met the acceptance criteria if the measured extension was within 2.75 mm ± 0.35 mm. The results showed needle extension below the maximum allowable length (2.75 mm) illustrating that at the most extreme extension the needles remain within specification.
- Needle penetration depth: The device was tested at 11 settings from 0 mm to 2.5 mm in 0.25 mm increments to evaluate all possible device parameters. Measurements were conducted to verify that the needle settings met the specified acceptance criteria of remaining within +0 mm/-0.25 mm of the selected needle depth. The results show that for each needle depth setting, the device was within the specified tolerance and met the pre-establish acceptance criteria. The testing verified the accuracy of the device parameters.

- Single use limit "Lockout": The device was tested to demonstrate that a key safety feature, the re-use protection feature built into the needle cartridge, functioned as intended. The feature prevents the single use needle cartridge from being detached and re-attached to the handpiece. To evaluate this feature, the cartridge was attached, detached, and re-attachment was attempted. The results showed that the cartridge could not be used a second time. Therefore, the re-use protection mechanism functions as intended to help prevent the risk of cross-contamination.
- Suction prevention: The device was tested to demonstrate that under simulated use the device does not produce suction. The results showed no visible signs of suction (*i.e*. circular marks), demonstrating that the needle cartridge design prevents suction during normal use.
- Micro-needle pull force test: Testing was completed to demonstrate that the needle cartridge can withstand a minimum force. A force gauge was used to record the force applied to the needles during testing. The cartridge was evaluated for forces > 110-gram force. The acceptance criteria were met if the inner and outer needles within the cartridge could withstand this minimum force. Results demonstrate that the needles can withstand forces greater than those encountered during normal use.
- Device use-life reliability: The device was evaluated over 2000 hours of use. This was representative of a use scenario of 4 hours a day, 5 days a week. The device motor and battery as well as the ability of the device to turn on and off were evaluated. The results confirm a use life of at least 2000 hours.
- Needle cartridge reliability: To further evaluate the needle cartridge, the needle cartridge was subjected to worst case use testing with a duration of testing more than double the typical clinical duration of use. In addition, an axial load was applied to the needle cartridge throughout the test. At the end of testing the cartridge showed no visual evidence of discoloration or damage to the inside of the cartridge. The test demonstrated the ability of the device to perform consistently under conditions of use.

LITERATURE REVIEW AND TRAINING MATERIALS

The SkinPen Precision System can achieve a maximum depth setting of 2.5 mm. As noted in the clinical section below, a maximum depth setting of 1.5 mm was evaluated in the clinical study to support the safety and effectiveness of the device for the treatment for acne scars on the face. To mitigate the risks associated with the parameters that were not evaluated clinically, a literature review was provided, including the results of three anatomical studies which assessed the depths and locations of superficial nerves and facial blood vessels[1,2,3]. The results of these studies demonstrated that the depth of motor and sensory nerves that could cause impairment were as deep as 26 mm and no shallower

[1] Rudolph R. "Depth of the facial nerve in face lift dissections." *Plastic and Reconstructive Surgery*. 1990;85(4):537-544.
[2] Christensen KN, Lachman N, Pawlina W, Baum CL. "Cutaneous depth of the supraorbital nerve: a cadaveric anatomic study with clinical applications to dermatology." *Dermatol Surg*. 2014;40(12):1342-1348.
[3] Lee J-G, Yang H-M, Choi Y-J, et al. "Facial arterial depth and relationship with the facial musculature layer." *Plastic and Reconstructive Surgery*. 2015;135(2):437-444.

than 2 mm[1,2]. The most superficial nerves, with depths around 2 mm were located in the periorbital area[2]. As noted in the section describing labeling below, the SkinPen Precision System contains a warning against treatment within the orbital rim and limits the depth for treatment of acne scars around the orbital rim to a maximum depth setting of 0.5 mm. For major facial blood vessels, the findings demonstrate that arteries are no shallower than 3-5 mm[4] from the skin surface. Therefore, a maximum penetration depth of 2.5 mm represents minimal risk, although the effectiveness for acne scar treatment at this depth is unknown. Included in the literature review was a retrospective analysis of over 550 patients treated with a similar device for a total of 3300 procedures[5]. The average depth of these treatments was 2-2.5 mm. Over 60% of the reported treatments were conducted on the face. There were no reports of adverse events that involved nerves or major vessels.

To further mitigate the risk of the unevaluated device parameters, a statement has been added to the labeling advising that depth settings greater than 1.5 mm have not been evaluated. In addition, training materials informing users of the locations of critical nerves and blood vessels and of the depth settings which have been determined to be safe is provided to each new device user.

SUMMARY OF CLINICAL INFORMATION

A clinical study was conducted to support the safety and effectiveness of the SkinPen Precision System for the treatment of acne scars on the face.

The study was conducted at a single center and included treatments on day 1, day 30, and day 60, with follow-up visits at 1 month and 6 months after the final (day 60) treatment. Treatments were conducted by a trained aesthetician (skin care specialist). The face was cleaned and numbed prior to treatment. A thin layer of Skinfuse Lift HG was applied prior to treatment to protect against abrasion and friction during the procedure. The aestheticians were instructed to start at the lowest depth setting and gradually increase the depth until erythema was observed, with a maximum depth of 1.5mm. The instructions included a precaution that microneedling could be used around but not within the orbital rim. The face was divided into quadrants for treatment to ensure that all acne scars were treated. Following treatment, Skinfuse Lift HG was applied to prevent the skin from drying out post procedure.

A total of 41 subjects completed the study. Only 20 of these subjects were treated with the SkinPen Precision System. The other 21 subjects were treated with a prototype device. There are technological differences between the SkinPen Precision System and the prototype device, including a greater number of needles in the SkinPen Precision cartridge and faster motor speed in the SkinPen Precision device, which may affect the device effectiveness results. Therefore, the safety assessments collected for both treatment groups are included in the summary below.

[4] Lee S., Gil Y. C., Choi Y. J., Tansati T., Kim H. J., Hu K. S. "Topographic anatomy of the superior labial artery for dermal filler injection." *Plastic and Reconstructive Surgery*, 2015; 135(2), 445-450.
[5] Sasaki GH. "Micro-Needling Depth Penetration, Presence of Pigment Particles, and Fluorescein-Stained Platelets: Clinical Usage for Aesthetic Concerns." *Aesthetic Surgery Journal*. 2017;37(1):71-83.

However, for the effectiveness results, only the data for the SkinPen Precision group was considered.

Subjects enrolled in the study included both men (31.7%) and women (68.3%) over the age of 21. The study included 11/41 subjects with Fitzpatrick Skin Type (FST) V and VI.

Table 3: Summary of Demographic Information

	SkinPen Precision System		All Subjects	
N	20		41	
Age (years)				
Mean (standard deviation)	43.8 (12.7)		44 (11.9)	
Minimum, Median, Maximum	23, 48, 60		21, 46, 60	
	N	(%)	N	(%)
Sex				
Male	7	35	13	31.7
Female	13	65	28	68.3
Ethnicity				
Hispanic or Latino	6	30	13	31.7
Not Hispanic or Latino	14	70	28	68.3
Race				
American Indian or Alaska Native	1	5	2	4.9
Asian	3	15	9	22.0
Black or African American	6	30	10	24.4
White	10	50	20	48.8
Fitzpatrick Skin Type				
II	2	10	3	7.3
III	4	20	10	24.4
IV	7	35	17	41.5
V	4	20	7	17.1
VI	3	15	4	9.8

The following is a summary of the important inclusion and exclusion criteria:
Inclusion Criteria:
To be eligible for study enrollment, a subject was required to satisfy each of the following criteria:

1. Men and women 18 to 60 years of age having general good health, with a maximum of 10% of subjects who were 18-30 years of age.
2. At least 20% of the subjects will have Fitzpatrick skin types IV-VI.
3. Individuals who have approximately 5 to 10 atrophic acne scars of mixed types (boxcar and/or rolling scars with some icepick scars allowed) on the face that are moderate to severe (grades 3 and 4 on Goodman and Baron's qualitative acne scar scale).

4. Individuals willing to withhold aesthetic therapies to the areas of the face being treated or judged to potentially impact results by the Investigator (*e g.* soft tissue fillers and/or any resurfacing procedures, botulinum toxin, injectable fillers, microdermabrasion, IPL (intense pulsed light), peels, facials, laser treatments, and tightening treatments, *etc.*) for the duration of the study. Waxing and threading is allowed but not facial laser hair removal.

Exclusion Criteria:
A subject was not eligible to participate if they met any of the following exclusion criteria:

1. Individuals who have presence of an active systemic or local skin disease that may affect wound healing.
2. Individuals who have severe solar elastosis.
3. Individuals with sensitivity to topical lidocaine.
4. Individuals who have a recent history or significant trauma to the face (< 6 months).
5. Individuals who have significant scarring, other than acne scars, in the area(s) to be treated.
6. Individuals who have severe or cystic active and clinically significant acne on the area(s) to be treated. Clinically significant acne was defined as a subject who has> 5 active inflammatory acne lesions (including acne conglobate, nodules, or cysts) in either the right or left treatment area.
7. Individuals who have a recent or current history of inflammatory skin disease, infection, cancerous/pre-cancerous lesion, unhealed wound or clinically significant acne in the proposed treatment areas. Individuals who have a history of systemic granulomatous diseases, active or inactive, (*e.g.* Sarcoid, Wegeners, tuberculosis, *etc*.) or connective tissue disease (*e.g.* lupus, dermatomyositis, *etc.*)
8. Individuals who currently have, or have a history of hypertrophic scars or keloid scars.
9. Individuals who have had microdermabrasion or glycolic acid treatment to the treatment area(s) within 1 month prior to study participation or who will have this treatment during the study.
10. Individuals who have a history of the following cosmetic treatments in the area(s) to be treated:
    - Skin tightening procedure within the past year;
    - Injectable filler of any type within the past;
        - 12 months for hyaluronic acid fillers (*e.g.* Restylane)
        - 12 months for Ca Hydroxyapatite fillers (*e.g.* Radiesse)
        - 24-months for Poly-L-Lactic acid fillers (*e.g.* Sculptra)
        - Ever for permanent fillers (*e.g.* Silicone, ArteFill)
    - Neurotoxins within the past 3 months;
    - Ablative resurfacing laser treatment;
    - Non-ablative, rejuvenative laser or light treatment within the past 6 months;
    - Surgical dermabrasion or deep facial peels:
    - Had a chemical peel, dermabrasion, non-ablative laser or fractional laser resurfacing of the face and neck within 4 weeks.
11. Individuals with a history of using any of the following prescription medications:
    - Accutane or other systemic retinoids within the past 6 months;

- Topical Retinoids within the past 2 weeks;
- Prescription strength skin lightening devices (*e.g.* hydroquinone, tretinoin, alpha hydroxy acids (AHA), beta hydroxy acids (BHA) and polyhydroxy acids, 4-hydroxyanisole alone or in combination with tretinoin, *etc.*) within 4 months;
- Any anti-wrinkle, skin lightening devices, or any other device or topical or systemic medication know to affect skin aging or dyschromia (devices containing alpha/beta/poly-hydroxy acids, vitamin C, soy, Q-10, hydroquinone; systemic or licorice extract (topically), Tego Cosmo C250, gigawhite, lemon juice extract (topically), emblica extract, *etc.*) within 2 weeks;
- Antiplatelet agents/Anticoagulants (Coumadin, Heparin, Plavix, chronic Non-Steroidal Anti-Inflammatory Drug (NSAID) use);
- Psychiatric drugs that in the Investigator's opinion would impair the subject from understanding the protocol requirements or understanding and signing the informed consent.

The study was initially designed to include primary endpoint assessment by the treating investigator using the Goodman and Baron's qualitative grading system for acne scar severity. However, this scale has not been validated for this outcome measure. A scale is validated if there is evidence that the instrument accurately measures what it is intended to measure. To utilize a validated scale and reduce investigator bias, the study design was revised during the study, such that 2 blinded evaluators would evaluate images after completion of the clinical study using the following assessment tools and timepoints [Table 4]. Details of each of these assessment tools are provided below in Tables 6-9. The results of the study are provided in Tables 10-14.

Table 4: Study Endpoints

Primary effectiveness endpoints	Acne Scar Assessment Scale graded by two blinded dermatologists using photographs taken at baseline, day 30, day 60, 1-month post-treatment, and 6-months post-treatment
	Clinician's Global Aesthetic Improvement Assessment graded by two blinded dermatologists using photographs taken at 1-month post-treatment, and 6-months post-treatment
Secondary effectiveness endpoints	Self-assessed Scar Improvement Scale completed by subjects at baseline, 1-month post-treatment, and 6-months post-treatment
	Subject Global Aesthetic Improvement Scale completed by subjects at baseline, 1-month post-treatment, and 6-months post-treatment
	Patient Satisfaction Questionnaire completed by subjects at 1-month post-treatment and 6-months post-treatment
Safety Endpoint	Subject safety diaries provided to the subject at each treatment visit (day 1, 30, and 60) and completed for 30 days to record treatment responses
	Adverse event monitoring at each visit; baseline, day 30, day 60, 1-month post-treatment, and 6-months post-treatment

At each clinical visit, digital images were taken of each subject's facial acne scars. On day 1, day 30, and day 60, imaging was performed prior to treatment. A total of 3 full-face images were collected. Images were also collected at the 1 month and 6-month follow-up visit. These images were graded by 2 separate Board Certified Dermatologists after completion of the study.

Table 5: Subject Accountability

	All Subjects	SkinPen Precision System
Enrolled subjects	N = 65	N = 33
Completed subjects (PP population)	41	20
Discontinued subjects	24	13
Reason for discontinuation		
Subject requested withdrawal	10	7
Lost to follow-up	3	1
Sponsor requested discontinuation[a]	11	5

[a]Sponsor requested for these subjects to be discontinued from the study for not having severe acne scars based on the images reviewed.

Of the 13 subjects who were discontinued from SkinPen Precision group of the study 12/13 discontinued prior to treatment. One subject received two treatments prior to discontinuation. This subject was appropriately followed after discontinuation. None of the discontinued subjects in the prototype group received treatment prior to discontinuation.

The photo grading included the following effectiveness assessments:

- Acne Scar Assessment Scale[6]

  Table 6: Acne Scar Assessment Scale

Grade	Term	Description
0	Clear	No depressions are seen in the treatment area. Macular discoloration may be seen.
1	Very mild	A single depression is easily noticeable with direct lighting (deep). Most or all of the depressions seen are only readily apparent with tangential lighting (shallow).
2	Mild	A few to several, but less than half of all the depressions are easily noticeable with direct lighting (deep). Most of the depressions seen are only readily apparent with tangential lighting (shallow).
3	Moderate	More than half of the depressions are apparent with direct lighting (deep).
4	Severe	All or almost all the lesions can be seen with direct lighting (deep).

  This scale was validated in a published study [1]. In the referenced study, live blinded evaluation was completed at 6-months post treatment. In the current study, this scale was used for photo grading by blinded evaluators at all timepoints.

[6] Jwala Karnik, Leslie Baumann, Suzanne Bruce, Valerie Callender, Steven Cohen, Pearl Grimes, John Joseph, Ava Shamban, James Spencer, Ruth Tedaldi, William Philip Werschler, Stacy R. Smith, "A double-blind, randomized, multicenter, controlled trial of suspended polymethylmethacrylate microspheres for the correction of atrophic facial acne scars." *Journal of the American Academy of Dermatology*. 2014;71(1):77-83.

- Clinician's Global Aesthetic Improvement Assessment (CGAIS)

Table 7: Clinician's Global Aesthetic Improvement Assessment (CGAIS)

Rating	Description
1	**Very Much Improved:** Optimal cosmetic result in this subject.
2	**Much Improved**: Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
3	**Improved:** Obvious improvement in appearance from initial condition, but a re-treatment is indicated.
4	**No Change:** The appearance is essentially the same as the original condition.
5	**Worse:** The appearance is worse than the original condition.

In addition to the clinician graded effectiveness measures, the following patient-reported measures were recorded throughout the study:

- Self-assessed Scar Improvement Scale

Table 8: Self-assessed Scar Improvement Scale

Rating	Description
-1	Exacerbation of Acne Scars
0	No change in appearance of acne scars
1	1% - 25% improvement in appearance of acne scars
2	25% - 50% improvement in appearance of acne scars
3	50% - 75% improvement in appearance of acne scars
4	75% - 99% improvement in appearance of acne scars

- Subject Global Aesthetic Improvement Scale

Table 9: Subject Global Aesthetic Improvement Scale

Rating	Description
1	**Very Much Improved**: Optimal cosmetic result.
2	**Much Improved**: Marked improvement in appearance from the initial condition, but not completely optimal.
3	**Improved**: Obvious improvement in appearance from initial condition.
4	**No Change**: The appearance is essentially the same as the original condition.
5	**Worse**: The appearance is worse than the original condition.

- Patient Satisfaction Questionnaire
  Three questions were asked to the subjects in the study regarding their level of satisfaction with the treatment. It was included as a secondary endpoint in the study. See individual questions and results in the section below.

Safety information was collected throughout the study using subject safety diaries. Safety diaries were provided to the subject at each treatment visit (day 1, 30, and 60). The subject was

instructed to record any observations related to treatment including common treatment responses. Common treatment responses are side effects that result from treatment which resolve on the order of days. Common treatment responses that persist may be categorized as adverse events when assessed by the investigator at the next visit.

Subjects were informed of the following potential common treatment responses in the informed consent process: skin will be red and flushed similar to a moderate sunburn, skin tightness and mild sensitivity to the touch, redness, burning, tingling, stinging, itching, and/or scaling/dryness, edema (swelling), tenderness/discomfort, a possibility of developing an infection (an increase in redness, warmth, itching, or pus formation). The diaries included space for daily recording of observations for the 30 days in between treatment visits. Adverse events were assessed by the investigator at each subsequent visit.

Results:

Safety:
At the 6-month post-treatment visit, no adverse events persisted.

The following common treatment responses were reported in the subject safety diaries which were sent home with the subject:

- Dryness in 5/41 (12%) subjects lasting from 1-6 days
  - These responses were reported by 3 subjects with FST III, 1 subject with FST VI, and 1 subject with FST V
- Rough Skin in 3/41 (7%) of subjects lasting from 1-2 days
  - These responses were reported by 1 subject with FST III, and 2 subjects with FST V
- Tightness in 2/41 (4%) of subjects lasting from 1-2 days
  - These responses were reported by 2 subjects with FST VI
- Redness, Itching, Peeling Discomfort and Tenderness in 13/41 (31%) of subjects lasting 1-3 days
  - These responses were reported by 6 subjects with FST III, 2 subjects with FST VI, 3 subjects with FST V, and 2 subjects with FST V
- Burning in 4/41 (9%) of subjects lasting 1-3 days
  - These responses were reported by 1 subject with FST III, 1 subjects with FST VI, and 2 subjects with FST V

Over the course of the study, 1 subject reported an arthropod bite on the inner right thigh that was determined to be moderate and unlikely related to SkinPen prototype device. One (1) subject (1/41, 2.4%) experienced an AE (skin striae [linear marks, ridges, or grooves] on the forehead and both sides of the face) that was determined to be mild and possibly related to use of the SkinPen Precision System. This AE was thought to be due to subject exposure to excess sunlight soon after treatment which was against study instructions, yet resolved without any additional complications.

Effectiveness:

Acne Scar Assessment Scale:
Results of photo grading using the Acne Scar Assessment Scale demonstrated that at baseline the mean population score was mild at 2.80. Following the three treatments and 6 months of follow-up, the mean population score was reported as mild at 2.35.

The evaluation by the blinded assessors indicated that seven subjects (7/20, 35%) had a 1-grade reduction in the Acne Scar Assessment Scale at 6-months post-treatment compared to baseline. The seven subjects reporting a 1-grade reduction included 1 subject with FST II, 2 subjects with FST III, 1 subject with FST IV, 2 subjects with FST V, and 1 subject with FST VI.

In addition, 4 subjects (20%) showed an improvement greater than 0 but less than 1 on the Acne Scar Assessment Scale, giving a total of 55% (11/20) of subjects showing improvement at 6-months post-treatment when compared with baseline. At 6-months post-treatment, the remaining 9 subjects (45%) reported no change in score when compared to baseline. The visual improvements seen in the photo grading results were considered to be clinically meaningful.

Table 10: Results of Photo Grading of Acne Scar Assessment Scale for SkinPen Precision System

Time Point	N	Mean	Standard Deviation	Minimum	Median	Maximum
Baseline	20	2.80	0.52	2.00	3.00	4.00
Day 30	20	2.78	0.57	2.00	2.75	4.00
Day 60	20	2.70	0.55	2.00	2.50	3.50
1-Month Post-Treatment	20	2.68	0.49	2.00	2.50	3.50
6-Months Post-Treatment	20	2.35	0.69	1.50	2.50	3.50

Table 11: Change from Baseline for Photo Grading of Acne Scar Assessment Scale for SkinPen Precision System

Time Point	N	Subject Improved (%)	Subject Worsened (%)	Mean Change	Standard Deviation for Change	Mean Change (%)
Day 30	20	30.0	20.0	-0.03	0.50	-0.9
Day 60	20	35.0	20.0	-0.10	0.50	-3.6
1-Month Post-Treatment	20	40.0	20.0	-0.13	0.58	-4.5
6-Months Post-Treatment	20	55.0	0.0	-0.45	0.46	-16.1

Clinician Global Aesthetic Improvement Assessment:
Analysis using the CGAIS was conducted by comparing the best and worst images of each subject as graded by the blinded dermatologists on the Acne Scar Assessment Scale. However, the best and worst were not chosen based on timepoint and therefore this endpoint was not considered to be clinically meaningful.

Self-assessed Scar Improvement Scale:
Treatment with SkinPen Precision produced an improvement in SASIS scores at 1 month post-treatment and 6-months post-treatment. At 1-month post-treatment, 17 (85%) subjects reported some percentage of improvement in the appearance of their acne scars, with 3 (15%) subjects

reporting no change. At 6-months post-treatment, 18 (90%) subjects reported some percentage of improvement in the appearance of their acne scars, with 2 (10%) subjects reporting no change. The mean values for the population were = 1.65 and 1.70, at 1-month post-treatment and 6-months post-treatment respectively (1%-25% improvement in appearance of acne scars) when compared with a score of 0 (no change in appearance of acne scars). No subjects reported a negative score (*i.e.*, exacerbation of acne scars) at either post-treatment timepoint.

Subject Global Aesthetic Improvement Scale:
Treatment with SkinPen Precision produced an improvement in SGAIS scores at 1 month post-treatment and 6-months post-treatment. At 1-month post-treatment, 7 (35%) subjects reported much improved, 9 (45%) subjects reported improved, and 4 (20%) subjects reported no change. At 6-months post-treatment, 2 (10%) subjects reported very much improved, 8 (40%) subjects reported much improved, 8 (40%) subjects reported improved, and 2 (10%) subjects reported no change. The mean values for the population were = 2.85 and 2.50, at 1-month post-treatment and 6-months post-treatment respectively (improved) when compared with a score of 4 (no change). No subjects reported a score of 5 (worse) at either post treatment timepoint.

Patient Satisfaction Questionnaire:
The results of the patient satisfaction questionnaire for all subjects indicated that a greater proportion of subjects selected favorable responses regarding treatments at 1 month and 6-months post-treatment for the following inquiries:

- Question 1: Do you notice any improvement in how your acne scars look in the treated area?

Table 12: Results of Patient Satisfaction Questionnaire - Question 1

Time Point	Yes [N (%)]	No [N, (%)]
1-Month Post-Treatment	16 (80.0)	4 (20.0)
6-Months Post-Treatment	18 (90.0)	2 (10.0)

- Question 2: How would you characterize your satisfaction with the treatment?

Table 13: Results of Patient Satisfaction Questionnaire – Question 2

Time Point	Extremely Satisfied [N (%)]	Satisfied [N (%)]	Slightly Satisfied [N (%)]	Neither Satisfied nor Dissatisfied [N (%)]	Slightly Dissatisfied [N (%)]	Dissatisfied [N (%)]	Very Dissatisfied [N (%)]
1-Month Post-Treatment	3 (15.0)	9 (45.0)	5 (25.0)	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)
6-Months Post-Treatment	3 (15.0)	9 (45.0)	5 (25.0)	1 (5.0)	1 (5.0)	1 (5.0)	0 (0.0)

- Question 3: Would you recommend this treatment to your friends and family members?

Table 14: Results of Patient Satisfaction Questionnaire – Question 3

Time Point	Yes [N (%)]	No [N, (%)]
1-Month Post-Treatment	18 (90.0)	2 (10.0)
6-Months Post-Treatment	18 (90.0)	2 (10.0)

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

Labeling has been included which consists of a user manual, instructions for use, box labeling, and patient labeling. The user manual and instructions for use include a description of the device technical parameters, relevant findings from the clinical study including common treatment responses. These documents summarize the main steps for using the device as well as the necessary measures to properly dispose of any single use items and clean the reusable components of the device.

The patient labeling includes information regarding how the treatment works, what to expect, and summarizes the findings of the clinical study in plain language.

The user manual, instructions for use, and box labeling include a precaution stating that the safety and effectiveness of the device has not been established at needle depths greater than 1.5 mm.

The following needle depths are recommended for treatment:

Table 15: Recommended Procedure Depths

Acne Scar Procedure Depth (Suggested Guidelines)	
Forehead (0.25 – 1.0 mm)	Nose (0.25 – 0.75 mm)
Around the Orbital Rim* (0.25 – 0.5 mm)	Facial Acne Scars (up to 1.5 mm)

*Note: Treatment can be performed around but not within the orbital rim.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a microneedling device for aesthetic use and the measures necessary to mitigate these risks.

Table 16: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	**Mitigation Measures**
Adverse tissue reaction	Biocompatibility evaluation Labeling
Cross-contamination and infection	Sterilization validation Reprocessing validation Non-clinical performance testing Shelf life testing Labeling
Electrical shock or electromagnetic interference with other devices	Electromagnetic compatibility testing Electrical safety testing Labeling

Identified Risks to Health	Mitigation Measures
Damage to underlying tissue including nerves and blood vessels, scarring, and hyper/hypopigmentation due to • Exceeding safe penetration depth • Mechanical failure • Software malfunction	Non-clinical performance testing Technological characteristics Shelf life testing Labeling Software verification, validation, and hazard analysis

SPECIAL CONTROLS

(1) The technical specifications and needle characteristics must be identified, including needle length, geometry, maximum penetration depth, and puncture rate.

(2) Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (i) Accuracy of needle penetration depth and puncture rate;
   (ii) Safety features built into the device to protect against cross-contamination, including fluid ingress protection; and
   (iii) Identification of the maximum safe needle penetration depth for the device for the labeled indications for use.

(3) Performance data must demonstrate the sterility of the patient-contacting components of the device.

(4) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the intended shelf life.

(5) Performance data must demonstrate the electrical safety and electromagnetic compatibility (EMC) of all electrical components of the device.

(6) Software verification, validation, and hazard analysis must be performed for all software components of the device.

(7) The patient-contacting components of the device must be demonstrated to be biocompatible.

(8) Performance data must validate the cleaning and disinfection instructions for reusable components of the device.

(9) Labeling must include the following:
   (i) Information on how to operate the device and its components and the typical course of treatment;
   (ii) A summary of the device technical parameters, including needle length, needle geometry, maximum penetration depth, and puncture rate;

(iii) Validated methods and instructions for reprocessing of any reusable components;
(iv) Disposal instructions; and
(v) Shelf life.

(10) Patient labeling must be provided and must include:
(i) Information on how the device operates and the typical course of treatment;
(ii) The probable risks and benefits associated with use of the device; and
(iii) Post-operative care instructions.

BENEFIT-RISK DETERMINATION

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study described above.

Adverse events (AEs) seen in the study included two subjects (3.1%) with a total of five non-serious AEs. One subject reported an arthropod bite on the inner right thigh that was determined to be moderate and unlikely related to SkinPen prototype device. One subject (1/41, 1.5%) experienced erythema, edema, and pruritus on the face that were determined to be mild and unlikely related to SkinPen Precision System and skin striae on the forehead and both sides of the face that was determined to be mild and possibly related to use of the SkinPen Precision System. This AE was thought to be due to subject exposure to excess sunlight soon after treatment which was against study instructions and resolved. The common treatment responses were dryness in 12% of subjects lasting from 1-6 days, rough skin in 7% of subjects lasting from 1-2 days, tightness in 4% of subjects lasting from 1-2 days, redness, itching, peeling, discomfort, and tenderness in 31% of subjects lasting 1-3 days, and burning in 9% of subjects lasting 1-3 days. These conditions all resolved. There were no serious AEs or reports of nerve and tissue damage. Although not seen in the clinical study, based on the literature, patients may experience reactivation of herpes simplex virus (cold sore), pigment changes that include lighter or darker skin in the area treatment that resolves over time, or no change in their acne scars. These adverse events and common treatment responses are included in the labeling.

The probable benefits of the device are based on nonclinical laboratory studies as well as data collected in a clinical study described above.

The indication for use to improve the appearance of facial acne scars is supported by the clinical study. There are many treatment modalities for the improvement of the appearance of acne scars: permanent treatments include laser, surgery (punch excisions), subcision, chemical peels, radiofrequency, and low energy light. Dermal fillers provide transient improvement. Lasers and chemical peel treatments have much higher risk profiles and patient recovery time but may provide more substantial improvement in the appearance of acne scars. These procedures are not typically performed on higher Fitzpatrick skin types due to the risks of pigment change. There are many treatments for improving the appearance of acne scars, because no single treatment works for everyone and some are much more invasive than others.

The SkinPen Precision System has a lower risk profile than some of the alternative treatments and as demonstrated in the clinical study can be used on Fitzpatrick Skin Type II-VI. Fitzpatrick Skin Type I was not assessed in the study; however, this is acceptable because patients with lower Fitzpatrick Skin Types are not at an increased risk of adverse events. The safety concern for this device is in the higher Fitzpatrick Skin Types who are at higher risk of transient and permanent pigment changes and scarring. The higher Fitzpatrick Skin Types were studied appropriately in the clinical study.

In this study, using the Acne Scar Assessment Scale, the two blinded assessors saw an improvement in 55% of patients at 6 months with the SkinPen Precision System with the mean scores improving from 2.8 at baseline to 2.35 at the 6 month follow up. No subjects had scars which were graded as worse at the 6 month follow up compared to baseline.

Patient reported outcomes demonstrated improvement in scar appearance and patient satisfaction.

Patient Perspectives

Patient perspectives considered for the SkinPen Precision System during the review included the following patient reported outcomes which were collected during the study:

- SASIS (self-assessed scar improvement) demonstrated an improvement in scores at 6-months post-treatment (mean value of 1.70 which is a 1-25% improvement in scars) when compared with a score of 0 (no change).
- Treatment with SkinPen Precision System produced an improvement in SGAIS scores at 6-months post-treatment (mean value 2.50 improved) when compared with a score of 4 (no change).
- The patient satisfaction questionnaire demonstrated improvement in acne scars (90% satisfaction or 18/20 patients), satisfaction with treatment (85% or 17/20 patients), and recommendation to family and friends (90% or 18/20 subjects) at 6-months post-treatment.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> SkinPen® Precision System is a microneedling device and accessories intended to be used as a treatment to improve the appearance of facial acne scars in adults aged 22 years or older.

The probable benefits outweigh the probable risks for the SkinPen Precision System. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the SkinPen Precision System is granted and the device is classified as follows:

Product Code: QAI
Device Type: Microneedling device for aesthetic use
Regulation Number: 21 CFR 878.4430
Class: II