May 16, 2018

NTK Enterprises, Inc.
Ms. Nancy Lockerman
Senior Vice President
2800 N Dallas Parkway, Suite 100
Plano, TX 75093-5994

Re: G170310/A001
Trade/Device Name: NTK Optimal Keratoplasty (Opti-K) System
Dated: April 11, 2018
Received: April 16, 2018
CMS Category: A
Annual Report Due: One Year from the Date of This Letter

Dear Ms. Lockerman:

The Food and Drug Administration (FDA) has reviewed the amendment to your Investigational Device Exemption (IDE) application regarding your feasibility study for a significant risk device. You have corrected the deficiencies cited in our January 19, 2018 disapproval letter. FDA has determined you have provided sufficient data to support initiation of a human clinical study; this means that there are no subject protection concerns that preclude initiation of the investigation. Your application is therefore approved, and you may begin your investigation after you have obtained institutional review board (IRB) approval. Your investigation is limited to 1 US institution and 30 US subjects.

We would like to point out that approval of an IDE application does not ensure that the results of this investigation will provide a reasonable assurance of the safety and effectiveness of your device or assure a determination of clearance/approval for your premarket submission.

FDA will waive those requirements regarding prior approval of a supplemental IDE application for investigational sites (21 CFR 812.35(b)) provided that the total number of investigational sites does not exceed the limit identified in this letter. Under this waiver, the study may be initiated at new sites, up to the approved limit, and updated information required by 21 CFR 812.20(b) on participating investigators and associated Institutional Review Boards (IRBs) and the IRB approval documentation may be submitted all at once in your IDE annual progress report. You must, however, submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the site limit specified in this letter. In addition, you must maintain current records as required by 21 CFR 812.140 and submit reports as required by 21 CFR 812.150. If a reviewing IRB requires any significant changes in the investigational plan or in the informed consent that may increase the risks to subjects or affect the scientific soundness of the study, then this change must be submitted to FDA for review and approval prior to initiating the study at that

investigational site (21 CFR 812.35). Minor changes requested by the IRB may be made without prior FDA approval. FDA also will waive the requirement for 6-month current investigator lists (21 CFR 812.150(b)(4)) provided that current investigator information is submitted every 12 months as part of the IDE annual progress report.

For clarification regarding FDA decisions and recommendations for IDEs, please refer to the FDA guidance "FDA Decisions for Investigational Device Exemption Clinical Investigations: Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff," available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf.

FDA has provided additional study design considerations as an attachment to this letter. These recommendations do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study. You are reminded that prior to implementing any significant modifications to the approved investigational protocol you must obtain FDA approval, and, if appropriate, IRB approval for the changes.

FDA encourages sponsors to collect clinical trial data in accordance with the Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126396.pdf) and to enroll patients that would reflect the demographics of the affected population with regard to age, sex, race and ethnicity. Reference is made to 21 CFR 812.25(c) regarding description of patient population and to 21 CFR 814.15(d)(1) with regard to the need for data, including foreign data, to be applicable to the U.S. population and U.S. medical practice. We recommend that you include a background discussion of prevalence, diagnosis and treatment patterns for the type of disease for which your device is intended. This should include sex- and race-specific prevalence, identification of proportions of women and minorities included in past trials for the target indication, and a discussion of your plan to address any factors identified or suggested, which may explain potential for under-representation of women and minorities, if applicable. We recommend that you include a summary of this information in your protocol and investigator training materials. Consideration should be given to enrollment of investigational sites where recruitment of needed populations for study can be more easily facilitated.

Future correspondence concerning this application should be identified as an IDE supplement referencing the IDE number above, and must be submitted in duplicate to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Information to help you understand the function and duties of a sponsor, titled, "Sponsor's Responsibilities for a Significant Risk Device Investigation," is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm. Additionally, information which you should provide to participating investigators, titled, "Investigators' Responsibilities for a Significant Risk Device

Investigation," is available at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049864.htm.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or other electronic media, accompanied by a signed cover letter and the complete original paper submission. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

For more information about FDA's eCopy program, including the technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf. In addition, we strongly encourage you to visit FDA's eSubmitter website at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm221506.htm in order to develop an eCopy in accordance with the technical standards prior to sending it to FDA.

Background regarding the assigned CMS category and the process for requesting re-evaluation of the category is provided in guidance: "FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions," which is available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm504091.pdf. Additional information about Medicare coverage related to Investigational Device Exemption (IDE) studies is available at https://www.cms.gov/Medicare/Coverage/IDE/index.html.

If you have any minor clarification questions concerning the contents of the letter, please contact Lawrence Kagemann at 301-796-6814 or Lawrence.Kagemann@fda.hhs.gov.

Sincerely,

Kesia Alexander

for Malvina B. Eydelman, M.D.
Director
Division of Ophthalmic and Ear, Nose,
and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure
Additional Recommendations and Considerations

ADDITIONAL RECOMMENDATIONS AND CONSIDERATIONS

The recommendations and/or considerations below do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study.

Study Design Considerations

FDA believes that additional modifications to your study design are needed. We recommend, but do not require, that you modify your feasibility study to address the following issues:

1. *In deficiency 6 regarding cases of significant decentration, we requested that you modify your protocol and case report forms (CRFs) to evaluate results from postoperative corneal topography, refractive astigmatism, visual acuity, patient questionnaire (primarily concerning diplopia) and compare these results to findings from those with centered treatments. While you state you will be using video capture on the treatment day, you did not modify your protocol to include analyses to address the aforementioned concerns. Because these analyses are important to help evaluate the risks associated with the use of your device, we recommend that you modify your protocol accordingly.*

Response. As reviewed in the protocol, in the first phase of the NTK Enterprises clinical study of Optimal Keratoplasty (Opti-K®) for low to moderate hyperopia correction (OK-001 IDE G080183 Use of Opti-K for hyperopia correction), mean decentration for the 10 eyes was 0.56 ± 0.34 mm, measured at the time of treatment. As there was concern for effects on vision, several key variables were studied. Coma: there was no statistically significant increase in induced coma except at the 3-month examination window. One eye was decentered by 0.93 µm leading to an induction of 0.68 µm of coma and a positive correlation between decentration and induced coma ($R^2 = 0.22$). Astigmatism: there was no statistically significant increase in astigmatism. Contrast sensitivity: there were no significant changes at any time period for any spatial frequency. However, with the improved centration technique, decentration has been markedly improved. In the U.S. OPTI-K-CVS-001 Centration Validation Study, the mean decentration measured was significantly reduced to 0.185 ± 0.135 mm (range 0.005 – 0.408 mm, N=20). In the continuation of the U.S. hyperopia trial, centration further improved to 0.107 ± 0.21 mm with all treatments < 0.2mm, our original target (Table 1). Going forward, we expect our improved technique will not lead to significant decentration. Nevertheless, we will "*evaluate results from postoperative corneal topography, refractive astigmatism, visual acuity, patient questionnaire (primarily concerning diplopia).*" However, since we do not expect to have treatments with significant decentration, we will not be able to "*compare these results to findings from those with centered treatments*." The protocol already specifies the collection of all the necessary examination data to fulfill the above evaluations. Centration and aberrometry assessment are not data required for entry on the case report forms as these data are determined through analysis of adjunctive records (video recordings and aberrometry examination data).

Table 1. Centration measurements for the 6 eyes treated for hyperopia in G080183.

Subject	offset, pxls	4 mm in pxl	decentration, mm
02-001	5	291	0.069
02-002	9	302	0.119
02-003	12	304	0.158
02-004	13	310	0.168
02-006	4	174	0.092
02-007	3	305	0.039
		mean	**0.107**
		sdtdev	**0.021**

2. *In response to deficiency 3, in Appendix B (Study Methods section) of the protocol you clarify the procedure for the Reading add determination. However, your instructions do not indicate whether the procedure is to be performed monocularly or binocularly, and do not indicate whether a subject is to initially have the distance manifest refraction in place while the plus lenses are to be added. We recommend that you modify this description to provide clarification.*

Response. Reading add determination should be made by measuring it monocularly in the eye to be treated. The reading add will be the amount of correction that is required, with the distance correction in place, to provide 2 lines of improvement in near acuity at 40 cm. The number of lines of improvement will be categorized postoperatively, i.e., what percentage of patients obtained one line, two lines, or three lines of improvement, as well as any that obtained more than three lines of improvement. As the primary outcome measure is improvement in near acuity, this could—depending upon each patient's individual needs—require a range of adds up to 2.5D.

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3. *In response to deficiency 5a, you modified section 9.7 of the protocol (clinical safety endpoint criteria) to change one of the examples of "serious and/or sight threatening events" that is related to intraocular pressure. This section now indicates "uncontrolled intraocular pressure (IOP) with increase of >10 mm Hg above baseline after medication or treatment, and any IOP above 25 mm Hg after medication or treatment" as a serious and/or sight threatening event. However, we are concerned that there may be many cases of a serious increase in IOP that will not meet these criteria "after medication or treatment." Therefore, we recommend that this example be changed as follows: "Elevation of IOP by >10 mmHg above baseline to a minimum of 25 mmHg."*

Response. The recommended change is made in the protocol: *"Elevation of IOP by >10 mmHg above baseline to a minimum of 25 mmHg."* IOP measurement will be made after the treatment.

4. *In response to deficiency 11, you have revised protocol Appendix B to describe the monovision tolerance test that investigators should implement with the subjects. In describing how to choose the contact lens, you state that "the contact lens will be AcuVue Oasis lens, a monofocal spherical lens with the dioptric power equal to the intended spherical adjustment of the eye to be treated." However, your protocol never indicates how to determine what the intended spherical adjustment of the eye will be. Furthermore, it appears that the expected adjustment will be the same for all subjects. We recommend that you modify the protocol to indicate what this expected adjustment should be for all subjects in the trial and modify the "monovision tolerance" section to indicate that the contact lens power should be chosen to be equal to this dioptric power.*

Response. The power of the Acuvue Oasis lens will be determined by the lowest power needed to obtain a gain of 2 lines in near vision at 40 cm. The goal of the procedure – and of this study – is an improvement in functional vision, not a specific dioptric change. That is why the goal is to provide 2 lines of improvement in uncorrected near vision

5. *In our letter from January 19, Study Design Consideration 1, we recommended that you provide instruction to investigators concerning specifying and recording the intended refractive change to be induced by the treatment. In addition, we indicated that you do not include a procedure concerning how to analyze the accuracy of the achieved treatment (i.e., change in manifest refraction spherical equivalent (MRSE) from baseline to the post-treatment time points. We recommended that you modify the procedures, CRFs, and study analyses to address these issues. You responded that you intend to conduct an analysis to determine the percent of eyes within 0.50D of the calculated shift. You also state that these data can be obtained from the current CRFs and has been added to the protocol. Please note that this does not address our original requested modifications to the protocol and associated*

documents. We recommend that you modify the study procedures, CRFs, and study analyses to provide instruction to investigators concerning specifying and recording the intended refractive change to be induced by the treatment, as previously requested.

Response. The intended refractive change will be greatest in the earliest post-operative period with gradual diminution to an induced MRSE myopic shift of >.75 D (on average) after one year as shown in Figure 1.1.5-1 of the protocol. A non-cycloplegic refraction will be performed at all visits to determine the percentage of eyes satisfying this intended endpoint. Functional visual acuity of two or more lines of near visual improvement is also an intended outcome This will be measured by Jaeger optotypes and the percentage satisfying this endpoint will be calculated.

6. *In response to Study Design Consideration 7, you state "inability to successfully dock the SAWSR for any reason is warned against in the instruction manual and is a reason to discontinue the subject from the study. Once the suction is applied to the SAWSR locking it into place, neither head nor eye movements will alter the centration." However, you have not provided evidence that the centration is not affected by these motion artefacts. We continue to recommend that your revise the CRFs to note and record any inadvertent head or eye movements during the procedure regardless whether these alter the centration of the SAWSR. This is intended to verify the potential effects of any observed movements on centration and/or treatment results.*

Response. The treatment CRF has been revised to note and record any inadvertent head or eye movements during the procedure, whether treatment had to be aborted for this or any other reason, and whether it was aborted before or during the treatment.

You may propose changes to address these Study Design Considerations as part of your feasibility study. If you intend to propose changes to your study to address these Study Design Considerations, you should submit an IDE supplement.

Future Considerations

In addition to the above concerns, you should give serious consideration to the following, which FDA considers important for the support of a future pivotal study:

1. *In response to deficiency 15, you state that the investigator cannot adjust the treatment based upon the dioptric change to achieve the needed reading add. We note that some of the potential subjects will receive minimal potential benefit in terms of presbyopia correction. For example:*

    a. *A subject with a non-dominant eye having a baseline MRSE of -0.50 D and needing an add of +1.00 D would only need a "needed spherical refractive change" of only +0.50 D, which is generally considered not enough to require treatment.*

    b. *A subject with a non-dominant eye having a baseline MRSE of +1.50 diopter and needing an add of +2.50 D would have a "needed spherical refractive change" of +3.50 D. However, you have indicated (in the email of 5-10-2018, Table 5) that the mean treatment effect is approximately 0.85 D. Therefore, it appears quite unlikely that this subject would achieve a substantial clinical benefit at 40 cm.*

    Please be advised that based on the results of your feasibility study, you may need to modify your inclusion criteria (see example below) and/or informed consent document to inform prospective study participants of anticipated results. For example, we recommend adding a criterion such as:

    The non-dominant eye must have a minimum "needed spherical refractive change" that is at least

+0.75 D and not greater than +2.50 D. (Where "needed spherical refractive change" = "Needed Reading Add" + Manifest Refraction Spherical Equivalent.) [The protocol would reference the section that defines "Needed Reading Add."]

You should also give serious consideration to the following comments that are intended to assist in your plans for a future marketing application. No response is necessary under this IDE, unless you wish to modify your device or study to address these concerns, in which case approval of an IDE supplement may be needed:

Response: New inclusion criteria in the protocol will include the following:

> The non-dominant eye must have a minimum of +.75 D but not greater than +2.5 D of spherical refractive change (i.e. Needed reading add + Manifest Refraction Spherical Equivalent).

The informed consent document will include the following:

> Opti-K was developed to help you see better up close without the need for glasses or contact lenses. However, our treatment produces varying degrees of near vision improvement consistent with the amount of improvement you require prior to treatment.
>
> While the vast majority of patients are expected to be able to read newsprint after the procedure, some may achieve the ability to read print as small in size as that found on a medicine bottle.

2. *Regarding your response to deficiency 16 related to light hazard analysis and protection, you provided testing and conformance to IEC 62471:2006. However, this standard is not adequate because it explicitly excludes lasers, in the wavelength range from 200 nm through 3000 nm and does not consider the combined total radiation exposure to the eye and retina from all light sources during an Opti-KTM System treatment. Therefore, at the time of a future marketing application, please address the element of total radiation exposure from all light sources. As previously indicated, we recommend that you utilize the ANSI Z80.36:2016 standard.*

Response: We agree that IEC 62471:2006 testing was for the other light emissions in the system. The laser safety, however, was tested, with the international IEC 60825-1 (2nd ed) standard. The test report starts after page 175 of the attached document. We are unsure of the specific differences between an ANSI standard vs. the IEC System for Conformity Testing and Certification of Electrical Equipment, but FDA has accepted the 60825 report in the past to assure laser safety. The 60825 report was required for the CE mark. Further, the ANSI Z80.36:2016 states: "ANSI Z80.36 does not apply to radiation that is intended for treatment of ocular tissues." Hence, we suggest that the international 60825-1 standard in addition to the IEC 62471:2006 should be sufficient to address the safety of all light sources during the treatment. ANSI takes the position "As with any standard, alternative validated test methods may be used."

FDA query: Is the IEC 60825-1 (2nd ed) acceptable?

3. Regarding your response to deficiency 17, you further explain and confirm that SAWSR suction produces an average increase of only 8.6 ± 0.7 mmHg in pig eyes. However, we do not believe there would only be a small intraocular pressure (IOP) elevation if the SAWSR does applanate the cornea to a diameter of over 11 mm. We are concerned that there may be artifactual considerations (e.g., scleral measurements with a tono-pen are not comparable to corneal measurements, or a leak in the eye allows fluid to be expressed out during applanation) that may have contributed to the results of your pig study. Alternatively, it is possible that your description of the SAWSR design is not sufficient such that we can understand why the IOP rise would be as small as 8.6 mmHg (e.g., the SAWSR window is a bowl- shaped surface that approximately matches the corneal curvature). Therefore, please provide additional details to explain the small IOP elevation, either by giving a more detailed and accurate description of the SAWSR system or by identifying and explaining the

reason(s) that may have contributed to inaccurate measurements. If the former, you should provide complete details to describe the SAWSR design and explain how you calculate the increase in IOP. If the latter, we recommend that you provide a discussion of your study design and/or updated results from testing based on addressing any possible confounding issues resulting from your set up.

Response. The Optimal Keratoplasty SAWSR has a 9.1 mm diameter sapphire window (Figure 1) that contacts the cornea under light manual pressure during the few seconds required for alignment/centering followed by application of a negative pressure to the suction ring to stabilize the SAWSR in place. (For comparison, the Intralase FS patient interface device window is 12-13 mm in diameter, sufficient to clearly show the limbus.) After centration of the SAWSR, suction is applied for 15.5 ± 1.8 seconds (N = 24; range 13-19; measured from randomly selected video recordings). During this period, the 2.5 second treatment is delivered, followed by a 2-3 second brief recorded inspection of the resulting pattern. As noted, our early data with enucleated and cannulated pig eyes recorded an average increase in intraocular pressure of only 8.6 ± 0.7 mmHg, a value which has been challenged. A similar experimental arrangement with enucleated pig eyes has been published by Vetter and colleagues[1] who compared IOP rises with 4 approved femtosecond lasers used for the creation of LASIK flaps in humans. When suction was turned on with the VisuMax laser, an increase in IOP of only 5 ± 2 (N = 12; range: 3 to 11) mmHg was recorded (Table 2; Vetter, et al.). The range of pressure increases reported for the 3 other lasers during suction application was 7 to 147 mmHg. Hence, the data reported in the early investigation with the Optimal Keratoplasty device, while low, is within the range found for 4 commercially available applanating femtosecond lasers using the same experimental ex vivo animal model. Owing to the potential for underestimating IOP rise in this model, we take 8.6 mmHg as the low end of the probable pressure rise during suction with the SAWSR.

The time period during which suction is applied is also potentially important for the assessment of device safety. The 4 lasers studied by Vetter, et al., required suction to be applied for between 64 and 166 seconds (Table 3; Vetter, et al.) compared to the range of 13-19 seconds required for the suction application time period for Optimal Keratoplasty.

In the Vetter investigations, the maximum average pressure measured ranged from 65 (VisuMax) to 205 mmHg (Table 4). Because retinal arterial occlusion can occur at pressures above the mean ophthalmic artery systolic blood pressure of ~95 mmHg with rapid, but temporary loss of vision, only patients being treated with the VisuMax are found to retain visual function during suction application. This is also the case for patients during application of suction with the SAWSR, clear evidence that the pressure rise with Optimal Keratoplasty is less than ~95 mmHg.[2] This is evidence that the high end of the pressure rise during suction application with the SAWSR is less than the pressure rise needed to occlude retinal perfusion and cause temporary loss of light perception as occurs with most femtosecond lasers except for the VisuMax.

In summary, the IOP rise during suction with the Optimal Keratoplasty SAWSR is short in duration and within the range that does not evoke loss of light perception during applanation.

[1]Vetter JM, Holzer MP, Teping C, Weingärtner WE, Gericke A, Stoffelns B, Pfeiffer N, Sekundo W. Intraocular pressure during corneal flap preparation: comparison among four femtosecond lasers in porcine eyes. J Refract Surg. 2011;27(6):427-433.
[2] da Silva FA, Krieglstein GK. [Measurement of ophthalmic blood pressure with the Mikuni dynamometer]. Klin Monbl Augenheilkd. 1980 May;176(5):764-72.

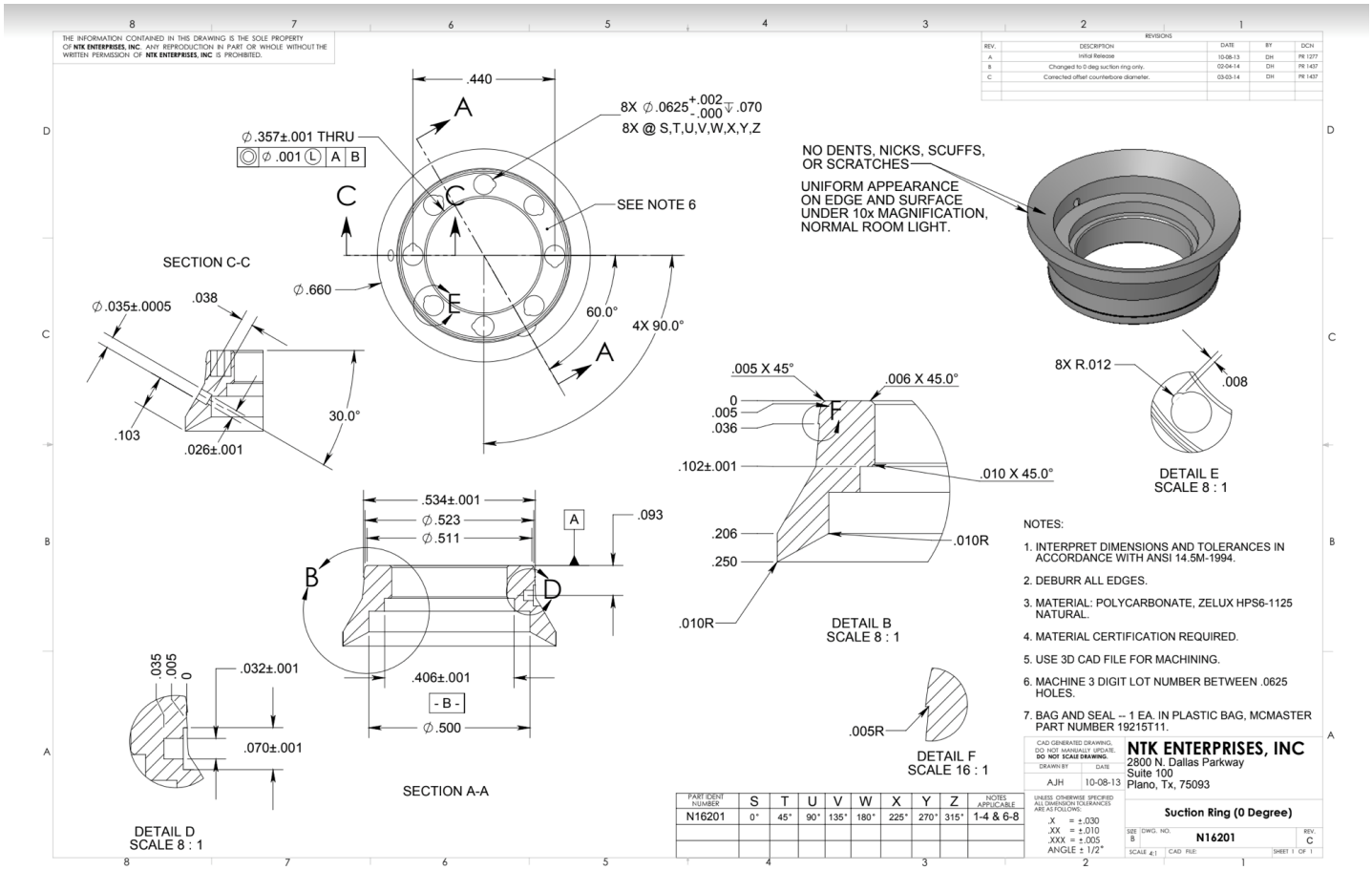

Figure 1. Mechanical drawing of SAWSR.