May 31, 2024

McKenzie E. Cato
Allyson B. Mullen
James P. Ellison
Hyman, Phelps & McNamara, P.C., on behalf of Nautilus Gloves LLC
767 5th Avenue 15th Floor
New York, NY 10153

Re: Docket Number: FDA-2024-P-0279

Dear Ms. Cato, Ms. Mullen, and Mr. Ellison,

This Final Response is to the above referenced request for reconsideration and petition for stay of action filed under 21 CFR 10.33 and 10.35 on January 11, 2024 ("Petition") on behalf of Nautilus Gloves LLC ("Nautilus").

A. Requested Actions

In the Petition, you request that the Commissioner of Food and Drugs ("Commissioner"):

1) "reconsider the Rescission, and instead permit Nautilus to amend the K210496 510(k) file with the correct In Vitro Cytotoxicity data for the Nautilus Nitrile Exam Gloves, thereby confirming the Agency's original finding of substantial equivalence."
2) "stay the Rescission pending reconsideration of the Rescission by the Commissioner."

B. FDA Decision

We have carefully reviewed your petition, as well as the exhibits thereto, and other information available to the Agency. For the reasons outlined below, we are denying your requests.

C. Background

On February 24, 2021, Nautilus submitted their premarket notification, K210496, for the Nautilus Nitrile Exam Gloves. In Section 15 of their 510(k), Nautilus states they conducted cytotoxicity testing and referred to Appendix B for supporting data. Appendix B includes the "In Vitro Cytotoxicity Test MTT Method Final Report" (pgs. 113-119 of 140 of the 510(k)) purportedly conducted on "Disposable Nitrile Examination Gloves" at the test lab "Shenzhen Boyuan Testing Technology Co. Ltd" with cell vitality results presented in Section 9.2 (pg. 118 of 140 of the 510(k)). The cell vitality results are presented in a table with 63 different values

including 56 "OD Values" reported to the thousandths place. On May 26, 2021, Nautilus received a substantially equivalent decision for their premarket notification, K210496, based on the submitted data.

On June 9, 2023, CDRH notified Nautilus of FDA's intent to rescind its substantial equivalence determination regarding Nautilus's device. CDRH provided the following basis for the intended rescission:

> [CDRH] has determined that it is appropriate to rescind the 510(k) [clearance] due to the misconduct involving the submission of biocompatibility data that appears to be duplicated as it is identical to data from another unrelated submission. If [CDRH] had known the data was duplicated and invalid at the time the submission was reviewed, the Agency would have rendered a not substantially equivalent determination.

CDRH further stated that Nautilus could either "respond in writing to [that] letter within 15 calendar days from the date of [that] letter to provide any information that [Nautilus] believe[s] may affect FDA's determination," or "request a regulatory hearing under 21 CFR Part 16 within 15 calendar days of the date of [that] letter."

On June 13, 2023, Nautilus responded, requesting a copy of the unrelated submission containing the biocompatibility data that CDRH referenced in its notice of intent to rescind (for ease of reference, this is also referred to as the "unrelated test report" in this response).

By email to Nautilus on June 14, 2023, CDRH stated that it would need to discuss Nautilus's request internally before providing a response.

On June 21, 2023, Nautilus requested a hearing under 21 CFR Part 16 and reiterated its request for a copy of the unrelated submission containing the biocompatibility data that CDRH referenced in its proposal to rescind.

On June 26, 2023, CDRH provided the following information to Nautilus:

> To elaborate further on the duplicated data, the Nautilus Gloves 510(k), K210496, provided (pgs. 113-119 of 140 of the submission) an "In Vitro Cytotoxicity Test" reportedly conducted at Boyuan Testing with cell vitality results in Section 9.2 (pg. 118 of 140 of the submission). However, the cytotoxicity data in this table are identical to the cytotoxicity data from another 510(k) submission. This other submission is for a different device type (i.e., not a glove) that uses a different material, a different color, and was both conducted and submitted to [FDA] before K210496. It is mathematically improbable that the K210496 data would be identical to the data in the other submission. Due to confidentiality concerns, we have decided not to share the other submission at this time.

On July 21, 2023, FDA provided additional information regarding the standard for granting a hearing under 21 CFR part 16 and further described the standard for denying a hearing under 21 CFR 16.26(a). Additionally, FDA stated that, if Nautilus intends to proceed with its June 21

hearing request, it should specify the grounds for that request by July 28, 2023. In response, Nautilus asked whether documents were needed to satisfy the standard under 21 CFR 16.26(a).

On July 28, 2023, Nautilus submitted additional arguments in support of its request for a hearing. In support of its request, Nautilus denied submitting duplicated data in its 510(k) submission.

On August 4, 2023, the Office of the Commissioner asked CDRH to respond to Nautilus's submissions, with a specific focus on whether Nautilus's submissions have raised a genuine and substantial issue of fact (*see* 21 CFR 16.26(a)) with respect to the proposed rescission.

In its response submitted on August 18, 2023, CDRH contended that Nautilus's submissions in support of its hearing request do not raise a genuine and substantial issue of fact warranting a hearing.

On September 5, 2023, Nautilus submitted its reply, and on October 12, 2023, Nautilus further supplemented that reply. Nautilus stated, "[T]he laboratory inadvertently inserted biocompatibility test results from another company's unrelated product in the In Vitro Cytotoxicity test report for Nautilus's product. Nautilus's agent did not identify the error[,] and, in turn, Nautilus included the unrelated product test result data in its 510(k) submission." Nautilus also attached the purported actual test results and stated that the information provided demonstrates a genuine and substantial issue of fact justifying a hearing on CDRH's proposed rescission.

On November 1, 2023, CDRH responded to Nautilus's October 12 reply stating that Nautilus's reply affirms that there is no genuine and substantial issue of fact meriting a hearing.

On November 28, 2023, FDA's Chief Scientist denied Nautilus's hearing request, finalized the Center for Devices and Radiological Health's ("CDRH") intent to rescind K210496, and directed CDRH to take the actions necessary to implement this decision based on its conclusion that there was no genuine and substantial issue of fact.

On December 12, 2023, CDRH accordingly sent Nautilus the recission letter, notifying the company that the Center has rescinded the substantial equivalence determination for K210496 that was ordered on May 26, 2021, and that the product has been removed from FDA's 510(k) Premarket Notification Database.

D. Discussion

D.1. Nautilus's Request to Reconsider the Rescission

In response to your request, FDA has reconsidered the Agency's rescission of K210496, taking into account your petition and the administrative record. We have determined that rescission was appropriate for the reasons set forth below.

Nautilus first argues that FDA lacks authority to rescind a 510(k) clearance, arguing that such actions are foreclosed by *Ivy Sports Medicine, LLC*, 767 F.3d 81 (D.C. Cir. 2014). We disagree.

Ivy Sports did not foreclose the use of FDA's inherent authority to rescind a 510(k) clearance where clearance information submitted by the sponsor affected the integrity of an agency's proceedings. Here, FDA is exercising this authority to rescind the clearance of a 510(k) notification where the information that formed the basis for the decision to clear the 510(k) notification was premised on invalid data provided by the sponsor. These facts are distinct from the facts in *Ivy Sports*, in that here the evidence provided to the Agency as part of the basis for the decision on the 510(k) clearance was invalid. The fact that the integrity of the Agency's proceeding was compromised by the invalid data submitted by the sponsor is not being contested.

Nautilus next argues that the rescission should be reversed because FDA has not "shown" any alleged misconduct. It further asserts that there was no misconduct – that the wrong biocompatibility data was submitted in the 510(k) file and that this was due to a clerical error. However, Nautilus and FDA agree that the information used to support the substantial equivalence order was invalid as it was "unrelated product test result data."[1] Due to this, the order finding the device to be substantially equivalent is no longer valid and, as such, must be rescinded. This is properly reflected in FDA's June 9, 2023 Intent to Rescind Letter. In that letter, FDA explained that had it known the data in the 510(k) was duplicated and not valid, it would not have rendered a determination that the device was substantially equivalent.

Regardless, there appears to have been misconduct by one or more entities that led to the submission of the invalid information. Some of the indications of misconduct are as follows:

Nearly Identical Test Report with Identical Procedures, Equipment, Reagents, Alphanumeric Identifiers, and Lot Numbers

- The Nautilus in vitro cytotoxicity test report is nearly identical to the unrelated test report, despite being tested by a different lab. The Nautilus testing was purportedly conducted by Shenzhen Boyuan Testing Technology Co. Ltd. ("BYT") located in Baoan District, Shenzhen. The unrelated test report is from a different test lab and a different city (*i.e.*, not BYT and not in Shenzhen). Yet, the substantive content of the Nautilus/BYT report beginning on page 3 to page 6 from "Section 1.0 Purpose" through "Section 12.0 Confidentiality Agreement" is nearly identical in format and order to that of the unrelated test report. While ISO 10993-5:2009 Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity provides extensive information on the sample/control preparation, preparation of cell culture, and test procedures, it is unlikely and improbable that two different test facilities would summarize the content in the exact same format and order.

- Even if there was a test report template that both BYT and the unrelated test report lab had access to, that would not explain the level of detail that is nearly identical between the two. The BYT and the unrelated test report are nearly identical, with all of the exact same "Lot Batch#" for the control articles, same instruments with the same alphanumeric identifiers, and same reagents with the same lot numbers.

[1] Suppl. Resp. to [CDRH's] Opp'n to Hr'g Req., Nautilus Gloves LLC, Oct. 11, 2023.

For example, in "Section 5.0 Equipment and reagents 1.1 Instruments" of the Nautilus/BYT test report, the instruments are reported as the following, with the alphanumeric identifiers in parentheses:

> Vertical pressure steam sterilizer (SHB026), CO2 Incubator (SHB002), Steel Straight Scale (SHB076), Electronic Balance (SHB016), Clean bench (SHB014), Multiskan Spectrum Microplate Spectrophotometer (SHB003), Bench type low speed centrifuge (SHB022), Inverted microscope (SHB005)

In "Section 5.0 Equipment and reagents 5.1 Instruments" of the unrelated test report, the same equipment is reported in the same order, with the same alphanumeric identifiers. It is improbable that two test facilities would use the same alphanumeric identifier convention as these would be decided by internal processes.

Evidence that Inclusion of Unrelated Test Report Was Not a "Clerical Error"

- The facts do not support Nautilus's explanation that there was a clerical error relating to the submission of its biocompatibility data. In the Petition, Nautilus asserts the biocompatibility data in its 510(k) submission was "inadvertently submitted to FDA due to a clerical error." Nautilus states in the Petition that it was "[un]aware that the BYT test report inadvertently contained data for a different product **BYT had tested** (not the Nautilus gloves), Nautilus included this test report in its February 16, 2021 510(k) submission and April 23, 2021 amended 510(k) submission" (emphasis added). Based on this information, we understand it is Nautilus's position that BYT had conducted both sets of tests – the one on Nautilus's product and the other on a different product. However, as detailed above, the test results submitted to FDA were for a different, unrelated device from a different test lab, located in a different city. Contrary to what Nautilus posits in its Petition, BYT did not test the unrelated product and these test results were not from BYT. This further supports that the submission of these test results to FDA was not a result of a "simple clerical error."

- Even if BYT and the unrelated test report lab followed the same test protocol, there is no plausible explanation for how an unrelated test of an unrelated device would result in identical numerical values for every result of the test. As previously stated, the unrelated test was for a different device type (*i.e.*, not a glove) and used a different material and, thus, should not have rendered identical test results. Even if the devices were made of the same material, it is improbable that there would be identical numerical values for every result of the test because of measurement variability between independent tests.

Evidence of Duplication: Irregularities and Errors Consistent with Optical Character Recognition, Transcription, and Manipulation

The Nautilus/BYT report contains the same typos as in the unrelated test report, which gives the appearance that the substantive content in the Nautilus/BYT test report was copied from

the unrelated test report. Further, the Nautilus/BYT report contains differences from the unrelated test report that, based on the nature of the differences, suggest that content from the unrelated test report might have been transcribed, albeit with some errors, and used for the Nautilus/BYT test report. These differences also suggest that the unrelated test report might have been scanned and converted to text using optical character recognition ("OCR") that resulted in some errors. FDA believes these differences would not occur from use of a template. We provide examples of the typos and differences below that suggest misconduct in the preparation of the Nautilus/BYT test report.

- "Section 1.2 Reagents" of the Nautilus/BYT test report lists "Penicillm-Streptomycm," which should be "Penicillin-Streptomycin," and "Tiyps in," which should be "Trypsin." Both of these reagents are spelled correctly in the unrelated test report. These differences appear to be due to scanning and OCR of the unrelated test report.

- The reagents in both the Nautilus/BYT test report and the unrelated test report list "Isopropyl alcoho". They both have the same unusual typographical error in the same place, as this reagent should be "Isopropyl alcohol". This is further evidence that the Nautilus/BYT test report duplicated the unrelated test report.

- Section 3.0 of the Nautilus/BYT report gives Lot Batch numbers for the negative control, positive control, and blank control, each of which is listed as having a different manufacturer. The Lot Batch numbers for the negative and blank controls are identical to the Lot Batch numbers for those controls in the unrelated test report. The nine-character alphanumeric Lot Batch number for the positive control is the same as the Lot Batch number for the positive control in the unrelated test report, except that one character is different and there is an added space between two characters. Additionally, the "Size" listed in the "Negative Control Article" of the Nautilus/BYT report is listed as "3 cmxlO cm" using a lowercase letter "l" and an uppercase letter "O" instead of numerical values. In the unrelated test report, the "Size" in the "Negative Control Article" is listed as "3 cmx10 cm," which uses numerical values correctly (*i.e.*, numbers are used to quantify and measure sizes, not letters). These differences appear to be due to scanning and OCR of the unrelated test report.

- In "Section 6.2 Test Method" of the Nautilus/BYT report, it states the following:

After the cells grew to about 70% and form a monolayer, original culture medium was discarded. The 96-well plates were then treated with 100 p l of extract of test article (100% 、 75% 、 50% 、 25%), control article, negative article and positive article respectively. The 96-well plate was incubated at 37 °C in cell incubator of 5% CO2 for 24 h. Six replicates of each test were tested.

After incubation, observe the cell morphology first and then discard the culture medium. Add 50 p l MTT (Img/ml) to each well and then incubated at *37 。C* in a humidified atmosphere of *5%* CO2 for 2 hours. The liquid in each well was tipped out and 100 p l Isopropyl alcoho was added to each well to suspend the cell layer. Evaluate the suspension above with a dual-wavelength spectrophotometer with the measurement wavelength at 570 nm.

In 3 separate locations, the test report includes an apparent Chinese character and "l" after a numerical value ("100," "50," "100"), which is nonsensical as these should be units. In "Section 6.2 Test Method" of the unrelated test report, the report indicates the correct units of "µl" for microliters. Additionally, the Nautilus/BYT test report captured above states the MTT concentration as "(Img/ml)" showing the letter "I" before "mg/ml." This is also nonsensical when considering that the test report of the unrelated submission states this as a numerical value "1" for "(1mg/ml)," which would be consistent with Clause C.2.2.4.3 of ISO 10993-5 that states "MTT is soluted fresh in MEM without supplements and without phenol red at a concentration of 1 mg/ml."

- In "Section 7.0 Statistical method" of the Nautilus/BYT report, it states:

Mean±standard deviation ($x \pm s$)

The cell cytotoxicity ratio = OD570 of test (or positive or negative) article group/ OD570 of blank control group x 100%.

This has an incorrect symbol for "mean" ("x"). In "Section 7.0 Statistical method" of the unrelated test report, the correct symbol for "mean" is used ("$\bar{x}$"). Additionally, the Nautilus/BYT report uses the incorrect notation for measuring optical density stating it as "OD570" twice. The unrelated test report uses the correct notation for measuring optical density "OD_{570}".

- In "Section 11.0 Record" of the Nautilus/BYT report, it states that "All raw data pertaining to this study and a copy of the final report are to be stored in the designated archive files at LIURUIRUI," which does not appear to be the name of a facility where data would be stored, although it possibly might be a person's name (*e.g.*, Liu Ruirui or Ruirui Liu). "Section 11.0 Record" of the unrelated test report states that the data will be held at the test facility and gives the name of the test facility. It appears the text was copied from the unrelated test report to the Nautilus/BYT report, but with what is presumably an odd error in changing from the name of a storage facility to the text "LIURUIRUI".

The above examples strongly support that there was misconduct in the preparation of the Nautilus/BYT test report. Specifically, Nautilus asserts that BYT had tested the unrelated product and there was a "simple clerical error", but this is not factually correct as BYT did not conduct the testing for the unrelated product. The observations above support that BYT used a copy of the unrelated test report and represented the report as testing conducted on the Nautilus Nitrile Exam Gloves. This explains why the test report format, order, equipment, equipment alphanumeric identifiers, reagents, etc. are nearly identical.

As demonstrated above, the Nautilus/BYT test report resulted from either the transcription and/or scanning of the unrelated test report using OCR, as there are numerous irregularities and errors consistent with our experience with character recognition software (*e.g.*, interpreting a number as a letter, incorrect symbols). In conclusion, the 510(k) submission for Nautilus's Nautilus Nitrile Exam Gloves contained biocompatibility data that appears to have been duplicated as it is nearly identical to data from another unrelated submission. Such data is, therefore, invalid and cannot be the basis for a substantial equivalence determination.

Accordingly, FDA rescission of the substantial equivalence order for the Nautilus Nitrile Exam Gloves (K210496) is supportable and warranted.

D.2. Nautilus Request for Amending K210496 510(k) with New Biocompatibility Data

In addition to requesting that FDA reconsider its decision to rescind K210496, Nautilus also requests that FDA "permit Nautilus to amend the K210496 510(k) file with the correct biocompatibility data, which would replace data inadvertently submitted to FDA due to a clerical error." For the reasons discussed below, FDA denies Nautilus's request.

FDA will not consider new data submitted in support of a 510(k) after it has issued an order finding a device to be substantially equivalent. A 510(k) submission must include all required elements to support a substantial equivalence finding, including such elements as the device description, the indications for use statement, the substantial equivalence discussion describing the different technological characteristics and the resulting performance testing, including the biocompatibility data. To have FDA make a substantial equivalence determination based on the new information Nautilus wishes to submit, Nautilus would need to make a new 510(k) submission. Moreover, as stated above, because it was based on invalid data, the order finding the device to be substantially equivalent is no longer valid and, as such, has been rescinded. With the rescission, Nautilus may make a new 510(k) submission following applicable procedures. If it does so, CDRH will review the 510(k) submission per the 510(k) process, including assessing the substance and validity of the new information.

Such review is important because these data were not part of Nautilus's 2021 marketing submission and have not been reviewed or verified by the scientific review team responsible for reaching a decision on substantial equivalence. The review for substance and validity will be particularly important in light of the appearance of misconduct by some entity in relation to the submission of the Nautilus/BYT in vitro cytotoxicity test report.

If Nautilus wishes to submit data to support a substantial equivalence determination, it may do so at any time by following the process set forth in section 510(k) of the FD&C Act and 21 C.F.R. Part 807 Subpart E.[2] FDA encourages Nautilus to leverage the Q-Submission Program to obtain FDA feedback prior to submitting a marketing submission.

D.3. Timeliness of FDA's Action

Nautilus's Petition further states "FDA did not take timely action to correct its 510(k) substantial equivalence decision via the rescission. To the contrary, in CDRH's August 18th opposition to a hearing, CDRH revealed that the duplicate data was discovered by CDRH in June 2022, a year before the Intent to Rescind letter was issued." Given the time-intensive, fact-specific nature of identifying, investigating, and documenting the data integrity issues, as well as the limited resources available during the COVID-19 pandemic, CDRH worked expeditiously on the

[2] Were Nautilus to pursue submission of a new premarket notification, CDRH staff would be glad to meet with Nautilus to discuss the Center's expectations relating to data integrity to help Nautilus avoid submitting fabricated or otherwise invalid testing data that would preclude CDRH from granting clearance.

rescission effort since first discovering the duplicative data in June 2022, following the administrative processes for such actions.

D.4. Nautilus's Petition to Stay the Rescission Pending Reconsideration

FDA may grant a petition for stay of action if the Agency determines such a petition is in the public interest and in the interest of justice (21 CFR 10.35(e)). FDA's regulation at 21 CFR 10.35(e) sets out the standard of review for a petition for stay of action as follows, in relevant part:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. . . . The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
>
> (1) The petitioner will otherwise suffer irreparable injury.
>
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
>
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
>
> (4) The delay resulting from the stay is not outweighed by public health or other public interests.

The filing of a petition for stay of action will not stay or otherwise delay any administrative action by FDA, including enforcement action of any kind, unless one of the following applies (*see* 21 CFR 10.35(d)):

> (1) The Commissioner determines that a stay or delay is in the public interest and stays the action,
> (2) A statute requires that the matter be stayed, or
> (3) A court orders that the matter be stayed.

As stated in the regulation, the Commissioner shall grant a stay if all four of the criteria above apply. We find that Nautilus has failed to demonstrate all four criteria. For the first criterion, the Petition states that "Nautilus will suffer irreparable harm from the 510(k) rescission, which has the effect of invalidating the 510(k)-cleared status of devices distributed by the company in reliance on the 510(k). This harm is exacerbated by FDA's delay in taking action on the discovered error, by waiting one year after identification of the duplicate data before pursuing a rescission." However, this is simply a conclusory statement and Nautilus fails to provide information on how it will suffer irreparable harm.

Further, Nautilus fails to address or provide any information at all about the second, third, and fourth criteria. The second criterion requires the petitioner to establish that its case is not frivolous and is being pursued in good faith. However, Nautilus has been provided ample

information regarding the invalidity and duplication of the data in its 510(k) submission to assess its case, yet Nautilus continues to assert the error was simply clerical without providing a reasonable explanation for the issues FDA has identified in the Nautilus/BYT test report and continues to ask the same questions seemingly expecting a different response.

For the third criterion, the petitioner must demonstrate sound public policy grounds supporting the stay. FDA believes Nautilus would not be able to demonstrate sound public policy grounds that would support staying a rescission of a substantial equivalence determination found to have contained biocompatibility testing data that was invalid and duplicated from another unrelated submission.

Finally, the petitioner must show that the delay resulting from the stay is not outweighed by public health or other public interests. It is in the interest of the public that 510(k) submissions for devices contain valid and accurate data and that FDA uphold such requirements so that it can accomplish its mission under Section 1003 of the Federal Food, Drug, and Cosmetic Act, assuring that devices are safe and effective. As such, FDA believes Nautilus will not be able to show that staying the rescission of K210496 510(k) is outweighed by the public health or public interests. As noted above, it was appropriate to rescind the substantial equivalence order because the order was invalid due to it having been based on a 510(k) submission that contained invalid data. Moreover, FDA does not know whether Nautilus's gloves at issue meet the standard for an order finding them substantially equivalent. For that, FDA would need to review and evaluate the new information. Even if the rescission – which has already occurred – could somehow be stayed such that the substantial equivalence order would remain in place while FDA reviews the new information, that would incorrectly convey that FDA considers the product substantially equivalent. Due to the invalid data, the substantial equivalence order is invalid; and in the absence of valid data, FDA does not know whether Nautilus has shown the product is substantially equivalent. Consequently, to the extent the petition is considered properly submitted under 21 CFR 10.35, we deny the request for a stay of action on these grounds.

FDA also has the discretion to grant a stay if it is in the public interest and in the interest of justice to do so. We decline to grant a discretionary stay of action on that basis because Nautilus has not established such action would be in the public interest or the interest of justice and, because we determined that the rescission was appropriate and that Nautilus can submit a new 510(k), we conclude that a stay would not be in the public interest or the interest of justice.

E. Conclusion

For the reasons discussed above, in accordance with 21 CFR 10.33 and 10.35, FDA denies your petition.

If you have any questions, please contact Gugandeep Kaur by e-mail at gugandeep.kaur@fda.hhs.gov.

Sincerely,

Lauren Roth -S

Digitally signed by Lauren Roth -S
Date: 2024.05.31 12:08:32 -04'00'

Lauren Roth, J.D.
Associate Commissioner for Policy
Office of the Commissioner
Food and Drug Administration