U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

Via Email
Return Receipt Requested

November 14, 2024

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Re: Aptar Radolfzell GmbH, Eigeltingen Site, FEI 3010236767

Dear Mr. Klofac, Mr. Fichert, & Ms. Hudson:

Thank you for your response to our June 2, 2023 email requesting additional items following the regulatory meeting held with your firm on May 8, 2023. We are also in receipt of additional correspondence, including your letter from August 8, 2023, with regard to your inspection classification as Official Action Indicated (OAI).

We have reviewed the documentation you provided to clarify your product and your role with supporting product design and testing for customers. Based on our subsequent review of information provided to date, it appears your (b) (4) is intended: (1) for use as a (b) (4), (2) to (b) (4) (b) (4) and (3) to (b) (4) (b) (4) drug product.

It also appears the (b) (4) is used as a component of a device. Based on the information you provided and the Agency's current thinking, we are removing the current good manufacturing practice (CGMP) OAI inspection classifications from U.S. Food and Drug Administration (FDA) databases. This includes removal of the OAI classification added in May 2024 for devices. This is because components of devices are not subject to the requirements of the Quality System regulation, and we generally do not subject them to drug CGMP requirements before they are incorporated into a drug's container/closure.

However, (b) (4) drug products, such as (b) (4), pose a heightened risk of harm to users because drugs applied to the (b) (4) (b) (4) (b) (4) is an important attribute for (b) (4) drug products (see (b) (4) As previously discussed with your firm, FDA remains concerned your (b) (4) may not be able to afford adequate protection from contamination for (b) (4) drug products without robust controls. There are numerous ways such presentations might fail to prevent microbial contamination. Any (b) (4) drug product that lacks adequate (b) (4) properties, when exposed to in-use contamination, is especially vulnerable to proliferation of microbes that can pose severe harm to consumers.[1]

You are responsible for providing components to customers that function and perform as intended, including meeting any agreed upon design and performance specifications. You note you perform some testing for your customers, which you characterize as usability testing. Depending on the precise nature of your testing (e.g., if it is intended to support or demonstrate drug formulation compatibility) and the expectations of the customer, you should consider whether you are operating as a contract manufacturer for an entity whose products - and outsourced manufacturing activities - are subject to the CGMP requirements of 21 CFR part 211.[2] In such a case, other requirements would apply as well, including the requirement to register as a drug manufacturer under section 510 of the Federal Food, Drug, and Cosmetic Act.

Particularly relevant CGMP requirements related to the use of your (b) (4) in combination products include the following:

- Employing suitable containers and closures (e.g., will maintain product sterility, will provide protection against foreseeable external factors in use)[3]

(b) (4)

[2] See FDA guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016), which discusses activities of the parties involved in contract drug manufacturing subject to CGMP requirements for drugs, available at https://www.fda.gov/media/86193/download.

[3] Refer to 21 CFR 211.94

- Formulating their drug products with a chemical (b) (4) or affording adequate protection during use[4]
- Performing appropriate supplier qualification activities (e.g., supplier agreements, supplier controls)[5]
- Testing as appropriate (e.g., satisfactory conformance for each batch, including sterility testing, (b) (4) effectiveness testing, stability testing)[6]

During the regulatory meeting on May 8, 2023, you stated it is not your responsibility but the customer's sole and exclusive responsibility to test the (b) (4) for compatibility with its container and product formulation, and that there is a disclaimer on all Aptar performance test reports clearly identifying all the responsibilities of your customers. If it is your firm's continued position that you have no responsibility for ensuring FDA's requirements for preventing contamination of drugs incorporating your product are met, we recommend you send a copy of this letter to all your customers that manufacture products incorporating your (b) (4) for the U.S. market. We also recommend you review your marketing/promotional materials to ensure they do not misleadingly suggest that finished product manufacturers do not need to conduct their own testing to determine the effectiveness of your (b) (4) in (b) (4) the sterility of drugs in products incorporating (b) (4). We also ask you send us copies of these customer notifications. If you do not plan to send this letter to all your customers, we request you notify this office in writing with your rationale.

Sincerely,

Francis Godwin -S

Digitally signed by Francis Godwin -S
Date: 2024.11.14 09:43:18 -05'00'

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

Copies:
Kimberly Y. Chainey, EVP, Chief Legal Officer and Corporate Secretary, AptarGroup, Inc., kimberly.chainey@aptar.com
(b) (4)

[4] Refer to 21 CFR (b) (4) and 21 CFR 211.94(b)
[5] Refer to 21 CFR 211.84
[6] Refer to 21 CFR 211.160, 211.165, 211.166