CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216016Orig1s000
216017Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 216016 and NDA 216017

REFUSAL TO FILE

Bracco Diagnostics Inc.
Attention: Patrice Marchildon
Senior Director, North America Regulatory Affairs
259 Prospect Plains Road, Building H.
Monroe Township, NJ 08831

Dear Ms. Marchildon:[1]

Please refer to your November 23, 2021 and December 10, 2021 new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Iomeron (iomeprol) injection for intravenous and intra-arterial administration.

After a preliminary review, we find your applications are not sufficiently complete to permit a substantive review. Therefore, we are refusing to file these applications under 21 CFR 314.101(d) for the following reasons:

CMC FILING ISSUES

We acknowledge your January 20, 2022 responses to the Drug Product and Manufacturing filing issues listed below. However, on review of your responses we find your applications are not sufficiently complete to permit a substantiative review.

Drug Product:

1. A clear description of your drug product was not provided in your application. Incomplete and contradictory information about your proposed marketed product presentations was submitted in Module 1, Module 2 and Module 3 - different strengths, containers, closures and fill volumes. According to your draft labeling, (b) (4) but this information is not provided in your description in Section 3.2.P.1 Description and Composition of the Drug Product or Section 3.2.P.7 Container Closure System, so it is not clear what products you intend to market in the United States.

   Per CFR 314.50(d)(1)(ii)(a), submit a clear and complete description of your proposed marketed products. Update Modules 1, 2 and 3 as needed.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

a. To Section 3.2.P.1 Description and Composition of the Drug Product, submit a table listing all the presentations that you propose to market. Clarify if the formulation is the same for all presentations or describe the different formulations.
b. For each presentation, include the container type, container volume, container material, container DMF(s), closures, closure material, closure DMF(s), strength and fill volume.
c. Identify each presentation as multi-dose, single-dose or pharmacy bulk pack.

2. Batch data for your drug product were not provided in your application. While we acknowledge that Section 3.2.P.5.4 Batch Analysis contains batch data, it appears that only one batch (#00560483, 400 mg I/mL fill presentation 50mL in 50 mL vial) may be representative of your (b) (4) proposed marketed product presentations. The remaining 5 batches submitted in this section (b) (4)) are not representative of your proposed marketed product as they differ in strength (e.g. (b) (4)), container size (e.g. (b) (4) or container type (e.g. (b) (4)). These batches appear to be your iomeprol injection products marketed outside the United States.

   For each presentation, submit batch data on three registration batches manufactured and packaged according to the process, formulation and container closure system submitted in your NDA, and also released according to the specifications and analytical methods submitted in your NDA.

3. Stability data for your drug product were not provided in your application. While we acknowledge that Section 3.2.P.8.3.1 Primary Stability Data contains stability data, it appears that only one batch (#00560483, 400 mg I/mL fill presentation 50mL in 50 mL vial) may be representative of your (b) (4) proposed marketed presentations. The remaining 5 batches submitted in this section (b) (4)) are not representative of your proposed marketed product as they differ in strength (e.g. (b) (4)), container size (e.g. (b) (4)) or container type (e.g. (b) (4)). These batches appear to be your iomeprol injection products marketed outside the United States.

   Per CFR 314.50(d)(1)(ii)(a), submit stability data for your proposed marketed product. For each fill presentation, submit primary stability data of at least 12 months duration under long term storage conditions on three registration batches manufactured and packaged according to the process, formulation and container closure system submitted in your NDA, and also released according to the specifications and analytical methods submitted in your NDA.

4. We advise you to request a CMC only meeting prior to resubmission to discuss how you propose to address these filing and review issues. Include any plans to support your proposed marketed product with data from your iomeprol injection

products marketed outside the United States – release, stability, extractables/leachables, batch records, etc. Include any plans to bracket your proposed marketed product.

Manufacturing:

5. Provide master batch records for all proposed strengths of the drug product and proposed commercial master packaging records per 21 CFR 314.54 (a)(1)(i) and 314.50(d)(1)(ii)(c).

6. In Section 3.2.R, provide executed batch production records (including the manufacturing and packaging records) for the drug product used to conduct primary stability study according the 21 CFR 314.50(d)(1)(ii)(b).

7. Provide translations for executed batch records which are not in English. Note that the executed batch record for the drug substance lot #2110415 is in Italian and the executed batch record for drug product #00570992 is in German. Translated versions were not provided.

8. Provide legible executed batch records. Note that the print was too faint to read for executed batch record #00571037, which was also in German with no English translation provided.

ADDITIONAL COMMENTS AND REQUESTS

We have the following additional comments and requests regarding your application that are not refuse to file issues. However, these comments should be addressed in your resubmission:

Drug Product

The following Drug Product information is needed for our review. Please include the following information when resubmitting your NDAs.

1. Submit photostability report with data to support your proposed container closure system, primary and secondary, and your label instructions to protect from light.

2. Submit freeze/thaw stability report with data to support temperature excursions.

3. Submit a table listing your proposed marketed product fill presentations to the container closure system file in Section 3.2.P.7 Container Closure System.

4. In a table, list the lots of drug substance and drug product used to conduct your pivotal clinical and non-clinical studies submitted to support evidence of the safety and efficacy of your proposed marketed product. Include the lot number, manufacture date and

location, manufacturer, formulation, strength, age of lot at time of administration, batch release data and presentation (container, closure and fill volume). Compare these lots to your proposed marketed product and describe differences. Submit this to your Drug Product file in Section 3.2.P.2.2 Pharmaceutical Development.

5. Confirm that all content submitted in your Quality Overall Summary (QOS) in Section 2.3 is also provided in Module 3. We note batches, not found in Module 3, are listed on p. 42 of the Drug Product file in QOS Appendix A. Iomeron Batch Information for Pivotal Clinical Studies. Update Module 3 as needed.

6. For ease of communication and review, title your tables with a unique table number and descriptive title identifying the table contents.

Manufacturing

7. Provide information in Section 3.2.P.3.3 or 3.2 P.2 listing all equipment used for bio/executed/registration and proposed for commercial batches. Include operation principle, capacity, and capacity utilization as applicable. Please provide a side-by-side comparison table listing all critical process parameters, their target with control limits for all the unit operations proposed for the commercial scale manufacturing, and the used/observed range from bio/executed/registration batches. All parameter control limits/target for the proposed commercial manufacturing should be justified based on product development studies (including scale up studies as necessary) and bio/executed/registration batch observations. Please also include the location in the application where study data is provided for all the critical process parameters.

8. Provide information listing all in-process tests, sampling plan, and acceptance criteria (target and/or range) proposed for the commercial scale manufacturing in addition, provide a summary table in 3.2.P.3.4 or 3.2.P.2 listing the in-process tests, sampling plans, and results (average, range, and RSD% as appropriate) for the bio/executed/registration batches. For each row, include in this table links to sections in the application where the information can be found. All in-process test specifications for the proposed commercial manufacturing should be justified based on product development studies and bio/executed/registration batch data.

Clinical

The following Clinical information is needed for our review. Please include the following information when resubmitting your NDAs.

1. Submit an Integrated Summary of Effectiveness (ISE) to module 5.3.5.3 of your applications. We note that in some cases the Summary of Clinical Effectiveness can serve as the ISE. Refer to the guidance documents “Integrated Summary of Effectiveness” (https://www.fda.gov/media/72335/download) and “Integrated Summaries of

Effectiveness and Safety: Location Within the Common Technical Document" (https://www.fda.gov/media/75783/download) for additional information on this topic.

2. Submit a rationale for assuming the applicability of foreign data to the U.S. population/practice of medicine.

3. Financial disclosure information is submitted in the flagship NDA 216017 but is not found in NDA 216016. Submit financial disclosure information to NDA 216016.

Please note that this filing review represents a preliminary review of the applications and are not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the applications.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the applications. A meeting package should be submitted with this Type A meeting request. To file these applications over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the applications be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The applications will be considered new original applications for user fee purposes, and you must remit the appropriate fees. If you choose to file over protest, FDA will generally not review any amendments to the applications and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of these applications.

If you have any questions, contact Ms. Sharon Thomas, Regulatory Project Manager, at 301-796-1994

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LIBERO L MARZELLA
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