CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216016Orig1s000
216017Orig1s000

PRODUCT QUALITY REVIEW(S)

CMC Memo for N216017 and N216016

To: File

From: Anne Marie Russell, Ph.D. Application Technical Lead

Re: Updated IQA Executive Summary - with new drug product data to support labeling

Final Overall Recommendation - Approval.

Action Letter Information - Expiration Dating: Stability data support an expiry of 24 months at 25ºC/60%RH when stored in the carton protected from light.

<table>
<tr><td>Product Information</td><td>New Molecular Entity 505b(2) application submitted by Bracco</td></tr>
<tr><td>Product Type</td><td>Sterile Injection</td></tr>
<tr><td>NDA Numbers</td><td>N216016 (intraarterial)
N216017 (intravenous)*
*all CMC information is in N216017.</td></tr>
<tr><td>Assessment Cycle Number</td><td>Cycle 1 after refuse to file</td></tr>
<tr><td>Drug Product (DP) Name and Strengths</td><td>Iomervu (iomeprol) injection – originally submitted as (b) (4)
<table>
<tr><td rowspan="2">Iomervu name</td><td colspan="2">Strength</td></tr>
<tr><td>mg iomeprol/mL</td><td>mg iodine/mL</td></tr>
<tr><td>250</td><td>51%</td><td>250</td></tr>
<tr><td>300</td><td>61%</td><td>300</td></tr>
<tr><td>350</td><td>71%</td><td>350</td></tr>
<tr><td>400</td><td>82%</td><td>400</td></tr>
</table></td></tr>
<tr><td>Route of Administration</td><td>injection</td></tr>
<tr><td>Drug Product Manufacturer</td><td>BIPSO GmbH Germany</td></tr>
<tr><td>Reference Listed Drug (RLD)</td><td>none</td></tr>
<tr><td>RLD/RS Number</td><td>none</td></tr>
<tr><td>Proposed Indication</td><td>Radiographic contrast agent for computed tomography (x-ray) imaging for several intravenous and intraarterial procedures of adult and pediatric patients.</td></tr>
</table>

Documents Assessed since IQA was archived	Date Received
SEQ 42 Quality amendment with density, molality and viscosity data	30-Oct-2024

Overall NDA Assessment: CMC is Adequate, PI issue is resolved.

Details: In the label, Bracco includes physical characteristics of their product in Section 11 of the Prescribing Information (PI) Table 6. Data to support the values of density, molality (not molarity as initially written) and viscosity for new and aged registration lots were expected, but had not been submitted at the time of archiving the IQA in Panorama on 26-Oct-2024.

Initial Assessment: Density, molality and viscosity are not critical quality attributes included in the drug product specifications. However, they are included in the PI and therefore data are required to support the reported values.

From the draft PI:

Table 6. Physical Characteristics of IOMERVU

Concentration (mg Iodine/mL)	Density ($d^{20}_4 \pm 0.0002$)	Osmolality (mOsmol/kg)	Viscosity (mPa·s)	
		37°C	20°C	37°C
250	1.278	435	4.9	2.9
300	1.334	521	8.1	4.5
350	1.390	618	14.5	7.5
400	1.446	726	27.5	12.6

Information Request Comment (Labeling) sent to Bracco:

1. *Physical Characteristics of Iomervu (PI Table 6)-*
    a. *Provide test data from newly manufactured and aged Iomervu registration batches to support the density, osmolarity and viscosity values reported in Table 6 of your draft Prescribing Information (PI).*
    b. *Provide a description of the test methods and pertinent information about the batches - e.g. lot numbers, manufacture date, age of lot when tested.*
    c. *If this information has been submitted, identify the location/documents where it can be found in your application (section, filename, pages).*
    d. *Provide a data-based scientific justification for excluding these attributes from release and stability testing programs or add them to your specifications.*

Response from Bracco - received 30-Oct-2024. Submitted product data from newly manufactured and aged lots to support Table 6 values. Data show some

variation within acceptable limits since these are not critical quality attributes or attributes with acceptance criteria specified in product specifications. See Appendix for data. Based on Bracco's 30 year historical knowledge of the product and process (ex-US), these attributes are not critical to quality control.

Final Assessment: Acceptable.

Appendix: Data (aged and release) to support PI Table 6 values for density, molality and viscosity.

Table L. Physicochemical Properties of Iomeron – Supportive Data

Conc. mgI/mL	Batch No.	Date of Manufacture	Age at time of testing (months)	Density (g/cm³) d^{20}_{4}		Osmolality (mOsM/kg)	Viscosity (mPa·s)	
				Release	Aged		20°C	37°C
250	00584184	24Jun2022	28					(b) (4)
250	00584183	24Jun2022	28					
250	00584185	27Jun2022	28					
Mean for Iomeron 250 (aged)				**1.2798**	**1.2798**	**457**	**5.4**	**3.1**
SD for Iomeron 250 (aged)				**0.0008**	**0.0014**	**1.0**	**0.1**	**0.0**
300	00582037	19Mar2022	31					(b) (4)
300	00583087	20May2022	29					
300	00584132	20Jun2022	28					
300	00582771	22Apr2022	30					
300	00583283	16May2022	29					
300	00583693	28May2022	29					
300	00583925	09Jun2022	28					
300	00583951	10Jun2022	28					
300	00584011	15Jun2022	28					
300	00582305	29Mar2022	31					
300	00582772	14Apr2022	30					
300	00583644	26May2022	29					
300	00583559	24May2022	29					
300	00583642	25May2022	29					
300	00584162	21Jun2022	28					
Mean for Iomeron 300 (aged)				**1.3360**	**1.3362**	**552**	**8.9**	**4.7**
SD for Iomeron 300 (aged)				**0.0010**	**0.0009**	**4.6**	**0.1**	**0.1**
300	4A72266	10Jan2024	9					(b) (4)
300	4E78317	01May2024	5					
300	4A73115	24Jan2024	9					
Mean for Iomeron 300 (newly manufactured)				**1.3346**	**NA**	**540**	**8.9**	**4.7**
SD for Iomeron 300 (newly manufactured)				**0.0020**	**NA**	**3.7**	**0.2**	**0.1**
350	00583694	30May2022	29					(b) (4)

Conc. mgI/mL	Batch No.	Date of Manufacture	Age at time of testing (months)	Density (g/cm³) d^{20}_{4}		Osmolality (mOsM/kg)	Viscosity (mPa·s)	
				Release	Aged		20°C	37°C
350	00584253	28Jun2022	28	(b) (4)				
350	00584232	28Jun2022	28					
350	00581501	26Feb2022	32					
350	00581555	02Mar2022	31					
350	00582306	31Mar2022	31					
350	00583358	11May2022	29					
350	00583359	11May2022	29					
350	00583360	13May2022	29					
350	00581480	23Feb2022	32					
350	00582303	28Mar2022	31					
350	00582304	29Mar2022	31					
350	00582127	22Mar2022	31					
350	00582128	23Mar2022	31					
350	00582810	26Apr2022	30					
Mean for Iomeron 350 (aged)				**1.3918**	**1.3924**	**655**	**15.9**	**7.6**
SD for Iomeron 350 (aged)				**0.0016**	**0.0014**	**10.1**	**0.3**	**0.1**
350	4A72632	22Jan2024	9	(b) (4)				
350	4A74431	18Jan2024	9					
Mean for Iomeron 350 (newly manufactured)				**1.3881**	**NA**	**634**	**15.3**	**7.4**
SD for Iomeron 350 (newly manufactured)				**0.0000**	**NA**	**2.3**	**0.0**	**0.0**
400	00584302	29Jun2022	28	(b) (4)				
400	00584303	29Jun2022	28					
400	00584304	29Jun2022	28					
400	00581554	01Mar2022	31					
400	00583285	16May2022	29					
400	00583692	27May2022	29					
400	00583779	02Jun2022	28					
400	00584143	16Jun2022	28					
400	00584144	17Jun2022	28					
400	00581460	22Feb2022	32					

Conc. mgI/mL	Batch No.	Date of Manufacture	Age at time of testing (months)	Density (g/cm³) d^{20}_{4}		Osmolality (mOsM/kg)	Viscosity (mPa·s)	
				Release	Aged		20°C	37°C
400	00583643	26May2022	29	(b) (4)				
400	00583742	02Jun2022	28					
400	00582083	21Mar2022	31					
400	00582639	14Apr2022	30					
400	00582942	26Apr2022	30					
Mean for Iomeron 400 (aged)				**1.4484**	**1.4490**	**788**	**32.0**	**13.4**
SD for Iomeron 400 (aged)				**0.0021**	**0.0021**	**11.2**	**1.1**	**0.1**
400	00602320	01Oct2024	1	(b) (4)				
400	00602321	02Oct2024	1					
400	4D6897	06Apr2024	6					
400	4G81777	18Jul2024	3					
400	4G81897	22Jul2024	3					
Mean for Iomeron 400 (newly manufactured)				**1.4436**	**NA**	**775**	**30.4**	**12.8**
SD for Iomeron 400 (newly manufactured)				**0.0006**	**NA**	**13.7**	**0.3**	**0.1**

NA = Not Applicable

Application Technical Lead: Anne Marie Russell, Ph.D.
Date: November 18, 2024

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/

ANNE M RUSSELL
11/18/2024 07:53:37 PM
Final recommendation from CMC: Approval

Integrated Quality Assessment (IQA) of New Drug Application

NDAs 216017 and 216017

Office of Pharmaceutical Quality

TABLE OF CONTENTS

NDA Executive Summary

1. Application/Product Information

NDA Numbers	216017 and 216016* *All CMC information for N216016 is submitted in N216017. This one IQA covers both sister NDAs.
Applicant Name	Bracco Diagnostics Inc.
Drug Product Name	Iomervu (iomeprol)
Dosage Form	Injection
Proposed Strength(s)	Iomervu name / Strength: mg iomeprol/mL / mg iodine/mL 250 / 51% / 250 300 / 61% / 300 350 / 71% / 350 400 / 82% / 400
NDA Classification	Type 1 - NME
Route of Administration	Intra-arterial (N216016)
Route of Administration	Intravenous (N216017)
Maximum Daily Dose	286 g iomeprol per image
Rx/OTC Dispensed	Rx
Proposed Indication	Diagnostic and interventional computed tomography & CTA procedures requiring intravenous administration of a radiographic contrast agent for both adult and pediatric patients.
Drug Product Description	Iomervu (iomeprol) injection is a contrast agent for CT imaging that is supplied as a sterile solution containing tromethamine (b) (4) hydrochloric acid (pH adjustment), and water for injection (b) (4) Thirteen presentations are packaged in clear glass single dose vials/bottles closed with a (b) (4) elastomer stopper and aluminum flip-off cap.
Co-packaged product information	N/A

Device information	N/A		
Storage Temperature/ Conditions	25ºC/60%RH stored in the carton protected from light		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joe Leginus	Sithamalli Chandramouli
	Drug Product/ Labeling	Anne Marie Russell	Danae Christodoulou
	Manufacturing	Zhouxi Wang	Kamal Tiwari
	Biopharmaceutics	N/A	N/A
	Microbiology	David Bateman	Laura Wasil
	Environmental Assessment	Xiaoqin Wu	James Laurenson
	RBPM	Anika Lalmansingh	
	ATL	Anne Marie Russell	
Consults	N/A		

2. Final Overall Recommendation - Approval, pending satisfactory resolution of the density, osmolarity and viscosity issue with Table 6 in the Prescribing Information (PI) labeling. See DP review.

3. Action Letter Information

a. Expiration Dating: Stability data support an expiry of 25ºC/60%RH when stored in the carton protected from light

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

NDA 216017, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product (b) (4) (iomeprol) injection strengths 250, 300, 350 and 400 in thirteen presentations. All information requests and review issues have been addressed, except for one pending drug product/labeling issue for which data are expected by the end of October 2024. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable

recommendation for all the facilities on Jul 3, 2024. Therefore, NDA 210617 and its sister application N216016, is recommended for approval from a Product Quality perspective, pending resolution of the drug product/labeling issue.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	**Adequate**
Drug Product	-	**Pending**
Quality Labeling	-	**Pending**
Manufacturing	-	**Adequate**
Biopharmaceutics	-	**Adequate**
Microbiology	-	**Adequate**

Environmental Assessment: **Review & FONSI - Adequate**

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: None

Comparability Protocols (PACMP): No

Comments: None

Additional Lifecycle Comments: N/A

SUBMISSIONS REVIEWED	SEQ	DOCUMENT RECEIPT	DISCIPLINE	TOPIC
Resubmission	9	Nov 30, 2023	all	Resubmission after refuse to file
Quality Amendment	11	Feb 29, 2024	DS Joe	DS heavy metals test 74 day letter
Quality Amendment	12	March 8, 2024	OPMA Josie	IR Feb 22, 2024 Process comments
Quality Amendment	15	March 26, 2024	OPMA Josie	IR Feb 22, 2024 Remainder of process comments
Quality Amendment	17	April 1, 2024	Pharm Tox	IR Feb 14, 2024 Qualifying impurity (b) (4)
Quality Amendment	18	April 4, 2024	EA Xiaoqin	IR Mar 1, 2024 Environmental assessment
Quality Amendment	20	April 15, 2024	Micro David	IR March 15, 2024 13 micro comments
Quality Amendment	21	April 17, 2024	DS Joe	IR April 3, 2024 DS limit for Impurity (b) (4) Data for Impurity (b) (4)
Quality Amendment	22	May 3, 2024	EA Xiaoqin	IR April 24, 2024
Quality Amendment	25	May 10, 2024	EA Xiaoqin	IR May 6, 2024 timeline for submitting fish study
Quality Amendment	27	May 23, 2024	Micro David	IR March 15, 2024 remainder of micro comments
Quality Amendment	28	May 30, 2024	Pharm Tox	IR April 24, 2024 DS and DP Impurity (b) (4)
Quality Amendment	31	June 27, 2024	DP Anne Marie	IR May 22, 2024 DP comparability, specifications, analytical procedures, Impurity (b) (4)
Quality Amendment	32	July 23, 2024	DP Anne Marie	IR July 9, 2024 DP (b) (4) testing, leachable study
Quality Amendment	37	Sept 11, 2024	EA Xiaoqin	Fish Study
Quality Amendment	38	Sept 24, 2024	DP Anne Marie	Labeling Table 6 in PI (density, viscosity and molarity)

Application Technical Lead Name and Date:
Anne Marie Russell, Ph.D.
Office of Product Quality Assessment II / Division of Product Quality Assessment IX
26-Sep-2024

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CHAPTER III: ENVIRONMENTAL

For more details about the items in this template, please see Chapter III (Environmental) of the NDA IQA Guide (OPQ-ALL-WI-0006)

R REGIONAL INFORMATION

1. Summary

The applicant submitted an environmental assessment (EA) in the original NDA 216017 & NDA 216016 for the drug product (b) (4) (iomeprol injection). The expected introduction concentration (EIC) of the active pharmaceutical ingredient (API) iomeprol is (b) (4) ppb, exceeding the categorical exclusion (CE) level of 1 ppb, thus an EA is needed, per 21 CFR 25.15(a) and 25.31(b).

The applicant requested the approval of (b) (4) to be used as a radiopaque medical imaging agent. (b) (4) is a non-ionic, monomeric, low-osmolar, radiographic contrast agent for use in major radiological diagnostic procedures, including selective coronary angiography and ventriculography; cerebral visceral and peripheral angiography; (b) (4) head and body computed tomography (CT); (b) (4) urography; (b) (4)

During the environmental review, FDA raised a concern over the API iomeprol's potential adverse effects on early life stage fish, based on FDA's read-across analysis of iomeprol's analogs, which are also iodinated contrast media (ICM). One of iomeprol's analogs, iohexol, was reported to have relatively high acute toxicity to fish embryos with a no observed effect concentration (NOEC) less than 10 ppb [1], which was over 8,000 times higher than its acute toxicity to fish juveniles (NOEC > 82 ppm) [2]. These results suggested that fish might be highly sensitive to ICM at the embryo early developmental stages, and iomeprol could also have the potential for causing toxic effects on fish embryos at the low ppb levels which could be close to its EIC. Considering this uncertainty in iomeprol's potential adverse impacts at environmentally relevant concentrations as well as its relatively high EIC, FDA recommended a chronic toxicity test of iomeprol on early life stage fish. The results may enable the Agency to meet the requirement to determine whether approval of this drug application would significantly affect the quality of the environment in the US, per 21 CFR 25.15(a).

To address FDA's concern, the applicant performed a chronic toxicity test on early life stage fish following the OECD 210 guidance and submitted a study report on September 12, 2024. Although the final revised EA will be submitted later in January 2025 via a post-marketing commitment (PMC), FDA concluded that the information

available thus far was adequate for the Agency to determine whether there would be significant environmental impacts due to the approval of this drug product application.

2. Substance of Interest

The drug product (b) (4) is formulated as a sterile aqueous solution (injectable liquid dosage form), containing the API iomeprol and inactive ingredients including tromethamine, hydrochloric acid, and water. (b) (4) also contains the following impurities: (b) (4) (b) (4)

The applicant stated that the above inactive ingredients were not regarded as dangerous to the environment. Also, the projected production of the by-products is less than (b) (4) kg/year which is much lower than the API iomeprol. Therefore, iomeprol was identified as the substance of interest in this EA.

3. Expected Introduction Concentration

The projected production of the API iomeprol is (b) (4) kg/year. The applicant accordingly estimated the EIC of iomeprol to be (b) (4) ppb following the FDA 1998 guidance [3].

4. Physicochemical Properties and Environmental Depletion

Iomeprol is a highly water-soluble chemical (70% w/w at 20 °C) with a low logK_{ow} value of –2.68 and a low vapor pressure (< 0.7×10^{-3} Pa at 30 °C and 2.1×10^{-3} Pa at 50 °C). It is expected to be readily photodegradable as its theoretical photolytic half-life is low (1.9 hours). In the aquatic environment, iomeprol is hydrolytically stable at environmentally relevant pH levels and is not considered readily biodegradable according to a closed bottle test result (15.2% biodegradation at 28 days).

Overall, iomeprol is expected to enter and remain in the aquatic environment once eliminated from the body and does not pass from the aquatic compartment to the atmospheric compartment. Thus, potential impact of the substance on the aquatic ecosystem is the primary environmental concern. Bioaccumulation and food-chain contamination are unlikely.

5. Environmental Effects

The applicant provided the following data showing the low ecotoxicity of iomeprol to microbes in activated sludge as well as to aquatic organisms including algae, aquatic invertebrate, and fish. The chronic toxicity test with zebrafish (*Danio rerio*) was conducted after the NDA submission and was not included in the initial EA.

Organism	Test duration	Endpoint	Toxicity value	Test method
Microbes in activated sludge	Not disclosed	Inhibition of the respiration rate	(b) (4)	Not disclosed
Freshwater green algae (*Selenastrum Capricormutum*)	Chronic (14 days)	Biomass and growth		OECD 201; FDA Environmental Assessment Technical Assistance Document 4.01
Aquatic invertebrate (*Daphnia magna*)	Acute (48 hours)	Immobilization; survival		OECD 202; FDA Environmental Assessment Technical Assistance Document 4.08
Bluegill sunfish (*Lepomis macrochirus*)	Acute (96 hours)	Mortality and sublethal effects		OECD 203; FDA Environmental Assessment Technical Assistance Document 4.11
Zebrafish (*Danio rerio*)	Chronic (35 days)	Hatching success; post-hatch survival; deformity and abnormal behavior in larvae; length and weight; etc.		OECD 210

6. Environmental Risk Assessment

In the initial EA, in which the recently conducted chronic toxicity test of iomeprol in zebrafish was not included, the applicant estimated the ratio of NOEC/EIC to be greater than (b) (4) This initial EA thus concluded that no adverse environmental effects associated with iomeprol released into the environment were identified and that no mitigation measures were needed.

Assessment: Adequate

Environmental Review:

The main goals of the environmental review, per 21 CFR 25.15(a) and (b) and 25.40, were to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment; and (2) if so, whether the proposed action will significantly affect the environment. Regarding the main findings of the EA:

- The substance of interest selection, which considered the API iomeprol as well as the inactive ingredients and impurities, was appropriate based on FDA 1998 guidance [3], which notes that the EA should list the drug or biologic substance and the predominant structurally related substances expected to enter or exist in the environment.
- FDA agreed with the estimation of iomeprol's EIC value ((b) (4) ppb). No refinement of the EIC was needed since iomeprol does not significantly deposit in tissues and is finally excreted unchanged in urine. Also, this EA didn't consider the wastewater treatment plant (WWTP) removal of iomeprol to refine the EIC, which was acceptable for a conservative risk assessment.
- Based on the physicochemical properties of iomeprol, FDA agreed that neither terrestrial or air compartment assessment was needed, and thus only the water compartment needed assessment. Iomeprol is expected to have low adsorption to activated sludge during wastewater treatment process and low potential for bioconcentration in aquatic organisms. Its risk to animals higher in the aquatic food chain is expected to be negligible. Although it may be readily photodegradable, iomeprol is potentially persistent in the aquatic environment as it is hydrolytically stable and not readily biodegradable. The frequent detection and relatively high measured concentrations of iomeprol in WWTP influents and effluents as well as surface water in Germany [4-7], where iomeprol has been approved for use for many years, also suggest that iomeprol may be environmentally persistent after being discharged from the WWTPs.
- The ecotoxicity studies and toxicity values of iomeprol provided by the applicant were acceptable. After the submission of the initial EA, the applicant conducted a chronic toxicity test using zebrafish *D. rerio*, following the OECD 210 guidance, to address FDA's concern over iomeprol's potential toxicity to early life stage fish. The test duration was 35 days, starting from newly fertilized eggs, and a variety of assessment endpoints were included as shown in the above table. No adverse effects were

observed at the test concentrations compared to the control group. The results showed that iomeprol had a low toxicity to fish embryos with a chronic NOEC of (b) (4) ppm. Iomeprol also had low acute/chronic toxicities to microbes in activated sludge, green algae *S. Capricormutum*, aquatic invertebrate *D. magna*, and bluegill sunfish *L. macrochirus*, with NOEC values ranging from (b) (4) ppm to (b) (4) ppm.

- Although the recently conducted fish early life stage test (OECD 210) has completed, the revised EA including the test results and an updated ecological risk assessment couldn't be completed within the review timeline and will be submitted later via a PMC. According to the submitted data, FDA estimated the predicted no effect concentration (PNEC) of iomeprol in the aquatic environment to be (b) (4) ppm and calculated the risk quotient (RQ) value to be (b) (4) (EIC/PNEC = (b) (4) ppb/ (b) (4) ppm), which is lower than the threshold value of 1. Therefore, iomeprol does not appear to have significantly adverse impact in the aquatic environment at the expected level of exposure, despite its potential for environmental persistence. FDA agreed with the applicant's conclusion that no significant adverse environmental effects were associated with iomeprol released into the environment and no mitigation measures were needed.

Overall Assessment and Recommendation:

Overall, the submitted information for environmental review (b) (4) was adequate. The information was sufficient to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment.

FDA concluded that no significant environmental impact was expected from the approval of NDA 216017 & NDA 216016. Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

Reference:

1. P. Yan, Z. Chen, S. Wang, Y. Zhou, L. Li, L. Yuan, J. Shen, Q. Jin, X. Zhang, J. Kang. Catalytic ozonation of iohexol with α-$Fe_{0.9}Mn_{0.1}OOH$ in water: Efficiency, degradation mechanism and toxicity evaluation. Journal of Hazardous Materials, 2021, 402, 123574.

2. N. Zhou, H. Liu, X. Yang, P. Watson, F. Yang. Disinfection byproducts of iopamidol, iohexol, diatrizoate and their distinct acute toxicity on *Scenedesmus sp*., *Daphnia magna* and *Danio rerio*. Chemosphere, 2023, 333, 138885.

3. US FDA. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. 1998. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications

4. UNESCO and HELCOM. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report. UNESCO Emerging Pollutants in Water Series – No. 1, UNESCO Publishing, Paris, 2017.

5. W. Seitz, W.H. Weber, J. Jiang, B.J. Lloyd, M. Maier, D. Maier, W. Schulz. Monitoring of iodinated X-ray contrast media in surface water. Chemosphere, 2006, 64, 1318-1324.

6. S. Pérez, D. Barceló. Fate and occurrence of X-ray contrast media in the environment. Analytical and Bioanalytical Chemistry, 2007, 387, 1235-1246.

7. J.L. Kormos, M. Schulz, T.A. Ternes. Occurrence of iodinated X-ray contrast media and their biotransformation products in the urban water cycle. Environmental Science & Technology, 2011, 45, 8723-8732.

Primary Environmental Assessor Name and Date: *Xiaoqin Wu, 9/18/2024*

Secondary Assessor Name and Date: *James P. Laurenson, 9/24/2024*

James Laurenson

Digitally signed by James Laurenson
Date: 9/25/2024 11:05:11AM
GUID: 51dc6bdb0000c62de59b85452e59746f

Xiaoqin Wu

Digitally signed by Xiaoqin Wu
Date: 9/25/2024 11:10:32AM
GUID: 625df66f00cc22833bedee13222a2cba

Finding of No Significant Impact

NDA 216017 & NDA 216016, [redacted](Iomeprol Injection)
[redacted]-250 (51%, 250 mg I/mL); [redacted]300 (61%, 300 mg I/mL); [redacted]
350 (71%, 350 mg I/mL); [redacted]-400 (82%, 400 mg I/mL)

Food and Drug Administration
Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications and supplements to such applications as an integral part of its regulatory process.

Bracco Diagnostics, Inc. requests approval of NDA 216017 & NDA 216016 for the drug product [redacted] which is used to produce contrast enhancement and facilitate the visualization of internal body structures using roentgen (X-ray) imaging modalities, such as angiography, [redacted] and computed tomography. The active pharmaceutical ingredient (API) of [redacted] is iomeprol, which is an iodinated contrast medium.

In support of its application, Bracco prepared an initial environmental assessment (EA) for [redacted] (attached) and later submitted a chronic toxicity study report for the API iomeprol to early life stage fish (attached). The initial EA as well as the study report evaluated the potential environmental impact from the use of [redacted]. The FDA Center for Drug Evaluation and Research (CDER) EA Team has reviewed the initial EA and the study report and has carefully considered the potential adverse effects due to approval of this application. FDA concluded that the submitted information was sufficient to determine significance, and thus the EA was adequate for approval, per 21 CFR 25.15(a).

Based on the review of the entirety of this information, FDA has determined that approval of these two NDAs is not expected to have a significant impact on the environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), per 21 CFR 25.15(b), and thus an environmental impact statement will not be prepared.

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James Laurenson

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Date: 9/25/2024 11:07:44AM
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Xiaoqin Wu

Digitally signed by Xiaoqin Wu
Date: 9/25/2024 11:10:42AM
GUID: 625df66f00cc22833bedee13222a2cba

CHAPTER IV: LABELING N216016 and N216017

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling	Assessor's Comments
Product Title in Highlights		
Established name(s)[1]	Adequate	IOMERVU (iomeprol)
Route(s) of administration	Adequate	injection
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Injection: 250 mg Iodine/mL, 300 mg Iodine/mL, 350 mg Iodine/mL, and 400 mg Iodine/mL
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	in single-dose vials or bottles
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”*	Adequate	Visually inspect IOMERVU for particulate matter or discoloration before administration, whenever the solution and container permit. Do not administer IOMERVU if particulate matter or discoloration is observed.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

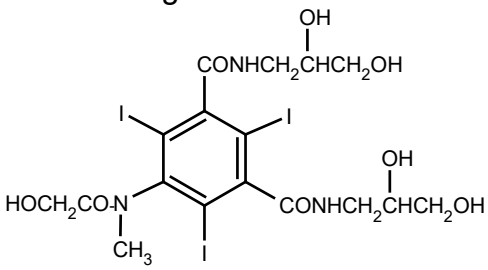
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

<table>
<tr><th>Item</th><th>Items in Proposed Labeling
(choose "Adequate", "Inadequate", or "N/A")</th><th>Assessor's Comments
(If an item is Inadequate, provide more details on the issues, as appropriate)</th></tr>
<tr><td colspan="3">DOSAGE FORMS AND STRENGTHS section</td></tr>
<tr><td>Available dosage form(s)</td><td>Adequate</td><td>Injection</td></tr>
<tr><td>Strength(s) in metric system</td><td>Adequate</td><td>available in the following iodine concentrations and configurations:
<table>
<tr><th>Concentration (mg Iodine/mL)</th><th>Package Size</th><th>Package Type</th></tr>
<tr><td>250</td><td>100 mL</td><td>Single-dose bottles</td></tr>
<tr><td>300</td><td>50 mL</td><td>Single-dose vials</td></tr>
<tr><td></td><td>100 mL, 150 mL, and 200 mL</td><td>Single-dose bottles</td></tr>
<tr><td>350</td><td>50 mL</td><td>Single-dose vials</td></tr>
<tr><td></td><td>100 mL, 150 mL, and 200 mL</td><td>Single-dose bottles</td></tr>
<tr><td>400</td><td>50 mL</td><td>Single-dose vials</td></tr>
</table></td></tr>
</table>

			100 mL, 150 mL and 200 mL	Single-dose bottles
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A			
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	clear, colorless to pale yellow solution		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A			
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose vials Single-dose bottles		

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	IOMERVU (iomeprol)
Dosage form(s) and route(s) of administration	Adequate	injection
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	tromethamine, hydrochloric acid.

<table>
<tr><td>For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.</td><td>Adequate</td><td>1 mg tromethamine
hydrochloric acid to adjust pH</td></tr>
<tr><td>If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol</td><td>N/A</td><td></td></tr>
<tr><td>Sterility statement (if applicable)</td><td>Adequate</td><td>sterile, nonpyrogenic</td></tr>
<tr><td>Pharmacological/Therapeutic class</td><td>Adequate</td><td>radiographic contrast agent for intravenous or intra-arterial use</td></tr>
<tr><td>Chemical name, structural formula, molecular weight</td><td>Adequate</td><td>The chemical name for iomeprol is N,N’-bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)-methylamino]-2,4,6-tri-iodo-1,3-benzenedicarboxamide. Iomeprol has a molecular formula of $C_{17}H_{22}I_3N_3O_8$, a molecular weight of 777.09 (iodine content of 49%), and the following structural formula:
  </td></tr>
<tr><td>If radioactive, statement of important nuclear characteristics.</td><td>N/A</td><td></td></tr>
<tr><td>Other important chemical or physical properties (such as pKa or pH)</td><td>Inadequate</td><td>
<table>
<tr><th colspan="5">Table 6. Physical Characteristics of IOMERVU</th></tr>
<tr><th rowspan="2">Concentration (mg Iodine/mL)</th><th rowspan="2">Density ($d^{20}_4 \pm 0.0002$)</th><th rowspan="2">Osmolarity (mOsmol/kg)</th><th colspan="2">Viscosity (mPa·s)</th></tr>
<tr><th>37°C</th><th>20°C</th><th>37°C</th></tr>
<tr><td>250</td><td>1.278</td><td>435</td><td>4.9</td><td>2.9</td></tr>
<tr><td>300</td><td>1.334</td><td>521</td><td>8.1</td><td>4.5</td></tr>
<tr><td>350</td><td>1.390</td><td>618</td><td>14.5</td><td>7.5</td></tr>
<tr><td>400</td><td>1.446</td><td>726</td><td>27.5</td><td>12.6</td></tr>
</table>
Not yet confirmed, awaiting data expected 30-Oct-2024. See DP review.</td></tr>
</table>

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	injection
Strength(s) in metric system	Adequate	Concentration (mg Iodine/mL) 250,300,350,400
Available units (e.g., bottles of 100 tablets)	Adequate	vials and bottles
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	clear, colorless to pale yellow solution
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single dose
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Protect from light. Do not freeze. 10 vials are stored in a carton that protects the product from light. Recommend "KEEP BOTTLES IN BOX WITH THE COVER CLOSED TO PROTECT FROM LIGHT" to replace "protect from light".

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store at 20°C to 25°C (68°F to 77°F)
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured for Bracco Diagnostic Inc. Monroe Township, NJ 08831 Manufactured by BIPSO GmbH 78224 Singen (Germany)

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

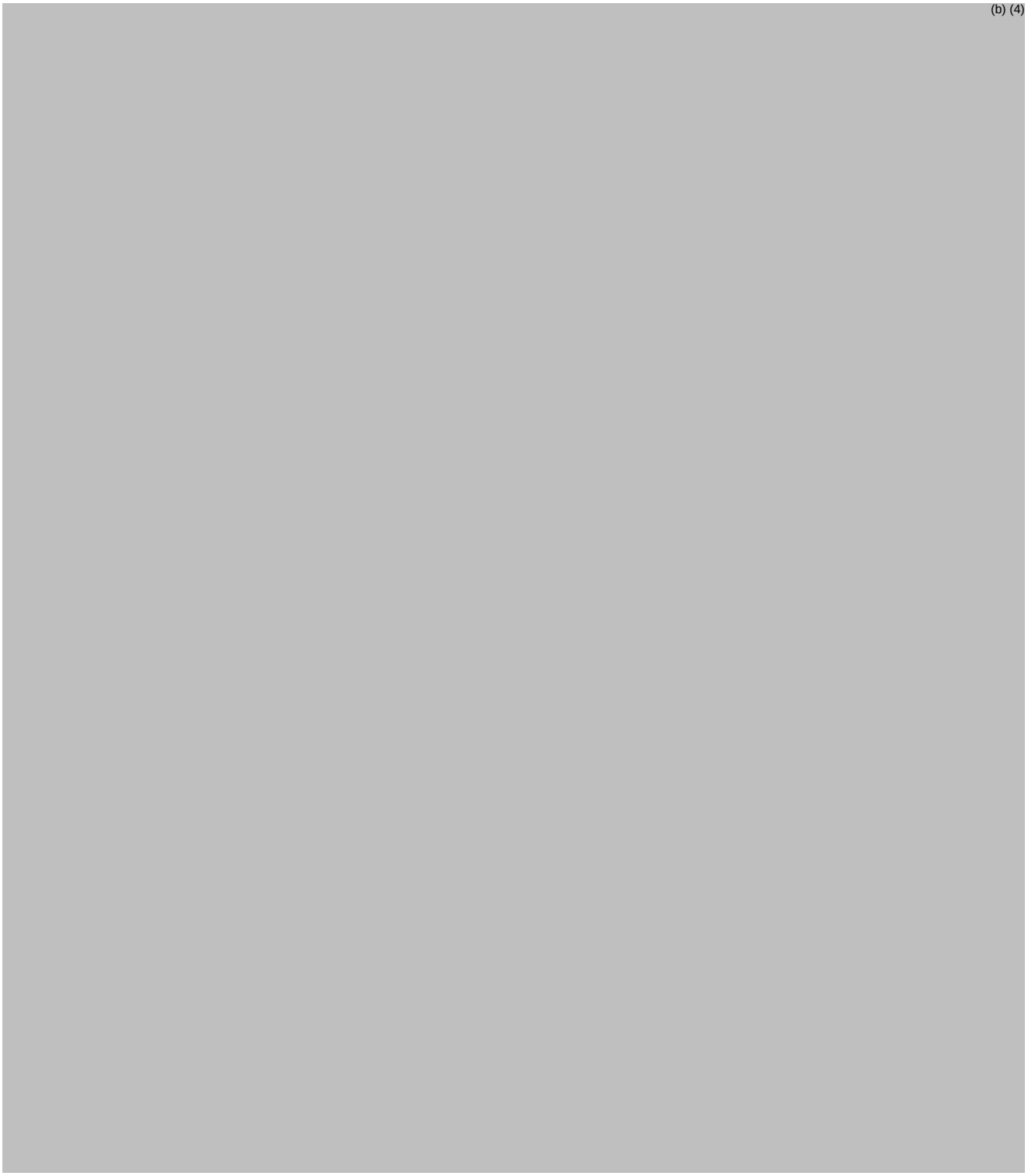
[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

Assessment of Carton and Container Labeling:

3.1 Container Labels

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

ITEMS FOR ADDITIONAL ASSESSMENT N/A

Overall Assessment and Recommendation: Adequate, pending resolution of the issue with Table 6 in Section 11 of the PI. Data expected 30-Oct-2024. See DP review. At this time, labeling negotiations are still ongoing with the applicant. OPQA will continue to provide CMC assessment for the final labeling.

Primary Labeling Assessor Name and Date:

Anne Marie Russell, Ph.D. CMC reviewer OPQ/OPQA II/DPQA IX

Secondary Assessor Name and Date

Danae Christodoulou, Ph.D. Supervisory Chemist OPQ/ OPQA II/DPQA IX

Anne Russell

Digitally signed by Anne Russell
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Danae Christodoulou

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	216017
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Iomeprol injection (b) (4) 250, 300, 350, 400 mg/mL Single dose bottle
Route of Administration	Intravenous injection
Applicant Name	Bracco Diagnostics Inc.
Therapeutic Classification/ OND Division	Division of Imaging and Radiation Medicine (DIRM)
Manufacturing Site	BIPSO GmbH Robert-Gerwig-Strasse 4 78224 Singe, Germany
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:
The drug product is (b) (4) (b) (4).

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0001	November 23, 2022
eCTD Seq #0009	November 30, 2023
eCTD Seq #0020	April 15, 2024
eCTD Seq #0027	May 23, 2024

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is supplied as a solution in 50 mL, 100 mL and 250 mL bottles all with 32mm stoppers.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents:

DMF (b) (4), dated August 7, 2023. (b) (4) (b) (4) (adequate)

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** The drug product is a sterile solution available in four strengths, 250 mg I/mL, 300 mg I/mL, 350 mg I/mL, and 400 mg I/mL in 50 mL, 100 mL or 250 mL bottles.

- The applicant provided the following summary table for the drug product composition (3.2.P.1, SEQ0009, Description and composition of the drug product, page 1)**:**

Table A. Composition of Iomeron

Ingredient	Unit	Formulation Concentration			
		Iomeron 250	Iomeron 300	Iomeron 350	Iomeron 400
Iomeprol	mg/mL	510 (b) (4)	612 (b) (4)	714 (b) (4)	816 (b) (4)
Tromethamine, USP/Ph. Eur.	mg/mL	1	1	1	1
Hydrochloric acid (b) (4)	mg/mL*	(b) (4)			
Water for injection, USP/Ph. Eur.	mL	q.s. to 1	q.s. to 1	q.s. to 1	q.s. to 1

* q.s. to pH adjustment

- The applicant provided the following summary table for the drug product container closure system (3.2.P.1, SEQ0009, Description and composition of the drug product, page 2)**:**

Table B. Primary Container Closure System for Iomeron Drug Product

Component	Description	Supplier	DMF
Vial/Bottle	USP/Ph. Eur. (b) (4) clear, colorless glass Nominal capacity 50-, 100-, 250-mL	(b) (4)	
Closure	(b) (4) elastomer (b) (4) 32 mm, dark grey, (b) (4) (b) (4)		
Flip-Off Caps	Aluminum- (b) (4) 32 mm (b) (4)		

- The applicant provided the following summary table for the drug product configurations (3.2.P.1, SEQ0009, Description and composition of the drug product, page 3)**:**

Table C. Iomeron Fill Presentations in Scope for the Current Submission

Iomeron Concentration	Fill Presentation (mL solution/mL nominal container capacity) – All presentations are single dose			
	50/50	100/100	150/250	200/250
Iomeron 250*	-	X	-	-
Iomeron 300	X	X	X	X
Iomeron 350	X	X	X	X
Iomeron 400	X	X	X	X

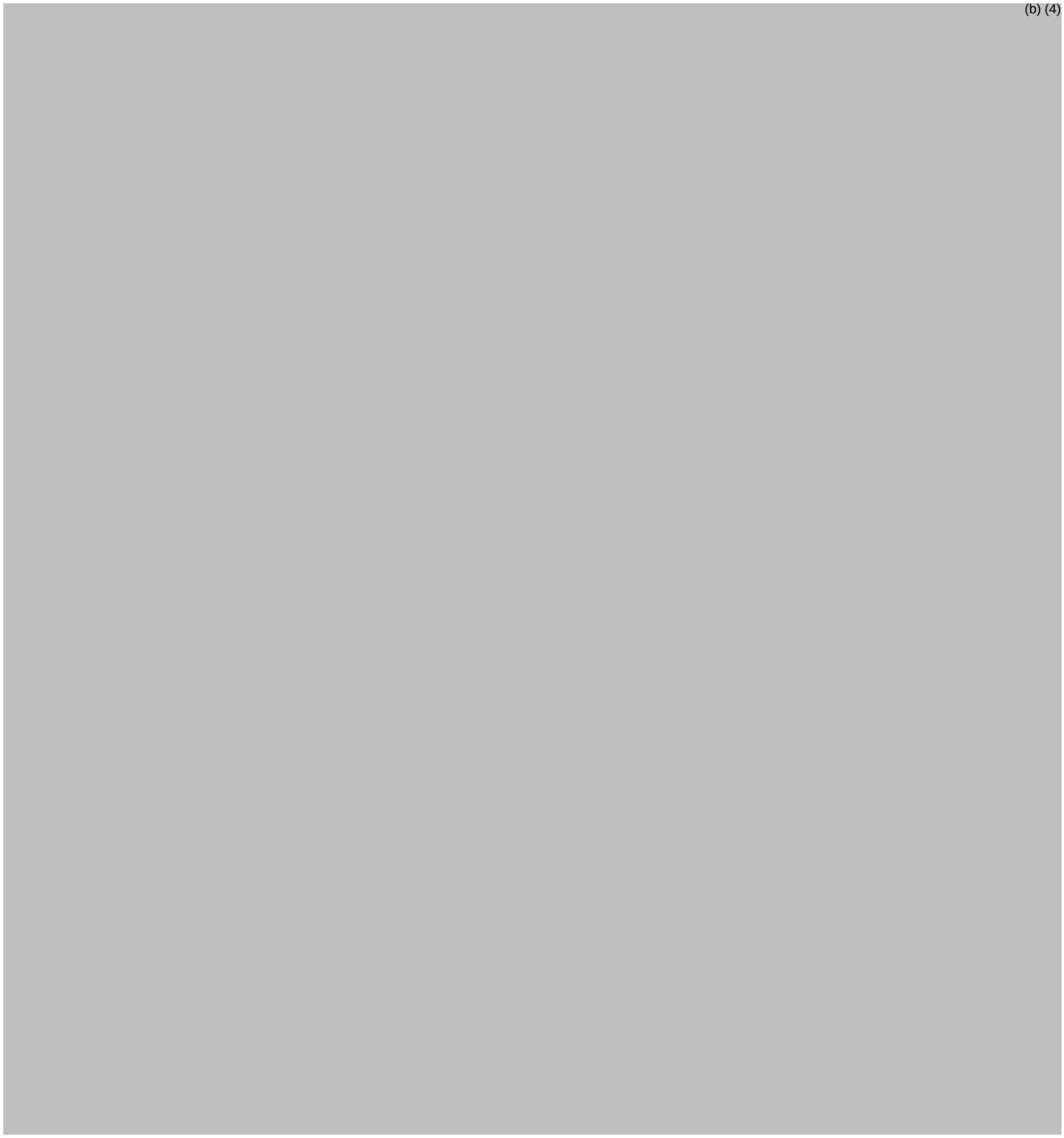
*NDA 216017 only

Adequate

Reviewer's Assessment:
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

(b) (4)



MICROBIOLOGY LIST OF DEFICIENCIES

None.

Primary Microbiology Assessor Name and Date:
David Bateman, Ph.D. (June 4, 2024)

Secondary Assessor Name and Date
Laura Wasil, Ph.D. (June 6, 2024)

Laura Wasil

Digitally signed by Laura Wasil
Date: 6/25/2024 12:31:05PM
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David Bateman

Digitally signed by David Bateman
Date: 6/25/2024 11:26:09AM
GUID: 5463e4f2002198d458a8bff3d150a8ed

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/

ANNE M RUSSELL
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N216017 and N216016