EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR X100 with Full Field Bone Marrow Aspirate (BMA) Application X100HT with Full Field Bone Marrow Aspirate (BMA) Application DECISION SUMMARY

I Background Information:

A De Novo Number

DEN230034

B Applicant

Scopio Labs Ltd.

C Proprietary and Established Names

X100 with Full Field Bone Marrow Aspirate (BMA) Application, X100HT with Full Field Bone Marrow Aspirate (BMA) Application

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
SAL	II	864.5261	Hematology

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for X100 with Full Field Bone Marrow Aspirate (BMA) Application and X100HT with Full Field Bone Marrow Aspirate (BMA) Application

B Measurand:

Specimen quality, blast cells, plasma cells, myeloid:erythroid (M:E) ratio

C Type of Test:

Sample quality assessment, blast and plasma cell estimation, and evaluation of myeloid lineage to erythroid lineage ratio estimation

III Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

X100 with Full Field BMA Application:
The X100 with the Full Field Bone Marrow Aspirate (BMA) Application is an automated cell locating device, intended for in vitro use only. The Full Field BMA application automatically locates and presents images of hematopoietic cells to trained operators for visual evaluation of Romanowsky stained bone marrow aspirate (BMA) smears. The Full Field BMA application assists trained operators to perform bone marrow smear quality assessment, blast cell, plasma cell, and M:E ratio estimation. A qualified operator must review, confirm or modify classification of each cell according to type, and verify results before finalizing and releasing the report.

The X100 with the Full Field Bone Marrow Aspirate (BMA) application presents images of Prussian Blue stained BMA smear.

X100HT with Full Field BMA Application:
The X100HT with the Full Field Bone Marrow Aspirate (Full Field BMA) Application is an automated cell locating device, intended for in vitro use only. The Full Field BMA application automatically locates and presents images of hematopoietic cells to trained operators for visual evaluation of Romanowsky stained bone marrow aspirate (BMA) smears. The Full Field BMA application assists trained operators to perform bone marrow smear quality assessment, blast cell, plasma cell, and M:E ratio estimation. A qualified operator must review, confirm or modify classification of each cell according to type, and verify results before finalizing and releasing the report.

The X100HT with the Full Field Bone Marrow Aspirate (BMA) application presents images of Prussian Blue stained BMA smear.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

X100 and X100HT Instruments

IV Device/System Characteristics:

A Device Description:

The X100 and X100HT instruments include a digital scanner and processing unit (computer) capable of acquiring high-resolution digital images from Romanowsky or Prussian Blue stained BMA slides with software application (Full Field Bone Marrow Aspirate (BMA) Application) for evaluation of acquired images. The X100 allows for three slides while X100HT comes with an additional component, a slide loader, a mechanical loading mechanism that holds up to 30 slides in three 10-slide cassettes and performs cover slipping and slide loading into the X100 scanner. The Full Field BMA application contains two scan modes - Romanowsky stain and Prussian Blue stain.

B Principle of Operation

The X100 / X100HT Scanner acquires image resolution that is equivalent to a manual microscope high power field magnification (100x). To acquire a high-resolution image, the sample slide is moved by the device's positioning stage under its main optic tube, which has a microscope objective with a tube lens and a high-resolution camera. An illumination system illuminates a light through the sample which is then collected by an optic tube. The optic tube is located on a vertical stage which assures focus throughout the scan. The device captures multiple images of the sample under a plurality of illumination conditions (different durations, illumination angles, illumination patterns, and wavelengths). The software application, Full Field Bone Marrow Aspirate (Full Field BMA) Application, suggests an analysis area, while taking into account the particulates in the area.

For Romanowsky-stained slides, the Full Field BMA Application automatically locates and presents images of hematopoietic cells on BMA smears. The Full Field BMA Application provides a Decision Support System (DSS) to assist in the evaluation of specimen quality, blast cell estimate, plasma cell estimate, and M:E ratio estimation. The DSS highlights a suggested result output for these parameters which a qualified operator would review and confirm before finalizing the report.

Parameter	How the parameter is evaluated	Results output
Specimen quality		
Sample quality	Qualitative	Adequate / Inadequate
		Particulate / Pauciparticulate / Aparticulate
		Adequate bone marrow / Diluted bone marrow (Hemodilute) / Bloody tap (Peripheral blood)
Stripped cells	Qualitative	Normal (<50%) / Increased
Blast		
Blasts Estimation	Qualitative	Normal (<5%) / Increased
	Semi-Quantitative	<5% / 5–19% /≥20%
Lymphoid Lineage		
Plasma cell estimation	Qualitative	<10% / ≥10%

Parameter	How the parameter is evaluated	Results output
Myeloid/Erythroid ratio		
M:E ratio	Qualitative	Normal / Abnormal / Too few to assess (Myeloid and Erythroid cells% < 50% out of total cells)
	Semi-Quantitative	Decreased / Normal [2–4:1] / Increased / Too few to assess

Parameters that do not have DSS suggestions and are manually identified by the operator are listed below.

Parameter	How the parameter is evaluated	Results output
Megakaryocytic lineage		
Estimation	Qualitative	Normal / Abnormal
		Decreased / Normal (2–10 Megakaryocytes per 10X field of view) / Increased
Maturation	Qualitative	Normal / Abnormal / Too few to assess (less than 30 MK)
Morphology	Qualitative	Normal (<10%) / Abnormal / Too few to assess (less than 30 MK)
Erythroid lineage - erythropoiesis		
Erythropoiesis Maturation	Qualitative	Normal / Abnormal / Too few to assess (less than 50 erythroid cells)
Erythropoiesis Morphology	Qualitative	Normal (<10%) / Abnormal / Too few to assess (less than 50 erythroid cells)
	Semi-Quantitative	<10% / 10–50% / >50% / Too few to assess (less than 50 erythroid cells)
Myeloid lineage		
Eosinophil estimation	Qualitative	Normal (<4%) / Increased
Basophil estimation	Qualitative	Normal (<1%) / Increased
Myelopoiesis Maturation	Qualitative	Normal / Abnormal / Too few to assess (less than 50 myeloid cells)
Myelopoiesis Morphology	Qualitative	Normal (<10%) / Abnormal / Too few to assess (less than 50 myeloid cells)
	Semi-Quantitative	<10% / 10–50% / >50% / Too few to assess (less than 50 myeloid cells)
Mast cell estimation	Qualitative	Normal (<1%) / Increased
Monocyte estimation	Qualitative	Normal (<2%) / Increased

Parameter	How the parameter is evaluated	Results output
Monocyte morphology	Qualitative	Normal (<10%) / Abnormal / Too few to assess (less than 20 monocytes)
Blast		
Blasts - Auer Rods detected	Qualitative	No / Yes
Blasts - Auer Rods detected	Qualitative	Single detection / Multiple detections / No Detections
Blasts - Granulation detected	Qualitative	No / Yes
Blasts - Nucleus morphology	Qualitative	Normal / Abnormal
Lymphoid lineage		
Lymphocytes estimation	Qualitative	Normal (<20%) / Increased
	Semi-Quantitative	<20% / 20–50% / >50%
Lymphocytes morphology	Qualitative	Normal / Abnormal
Plasma cell morphology	Qualitative	Normal / Abnormal
Prussian Blue stain smear analysis		
Storage iron - Specimen Quality -	Qualitative	Adequate / Inadequate
Storage iron - Iron Stores	Qualitative	Normal / Abnormal
		Decreased / Normal / Increased
Storage iron - Ring sideroblasts	Qualitative	No (<5%) / Yes
	Semi-Quantitative	<5% / 5–15% / >15%

For Prussian Blue stained slides, the Full Field BMA Application also scans and displays high-resolution images acquired from fixed and Prussian blue stained BMA smears. The scan is used by skilled users to provide grading of iron stores and ring sideroblasts based on Prussian Blue staining of the aspirate sample, without DSS suggestions.

The qualified user can either utilize the DSS suggestions or hide the DSS suggestions and work independently, by viewing the digital copy of the patient sample and performing a visual assessment of the various findings, as they would using an analog microscope, while documenting their findings in the digital report format provided by the Full Field BMA

Application. A qualified operator must review, confirm or modify classification of each cell according to type, and verify results before finalizing and releasing the report.

C Instrument Description Information

1. Instrument Name:

   The X100
   The X100HT

2. Specimen Identification:

   The slide's barcode is captured automatically and assigned to each case. The device also supports typing the barcode manually.

3. Specimen Sampling and Handling:

   A BMA smear is prepared within four hours following aspiration according to the protocols and procedures used per laboratory procedure. The slides are stained using Romanowsky or Prussian Blue stains. The BMA smear is covered with a cover slip using a clear mounting medium. The face of the slide should be cleaned in order to remove residues, oil and/or dust.

4. Calibration:

   The device is calibrated by a trained technician at the factory on a BMA slide. Re-calibration can also be performed by a certified technician if a problem arises during the daily quality control (QC) testing, which is determined as a calibration issue. The installation calibration tests consist of memory availability assessment, Z calibration to determine the exact height limit of the objective lens to obtain focused image, stage alignment calibration, movement calibration, and vibration testing.

5. Quality Control:

   The Full Field BMA software automatically initiates a QC test the first time a case is reviewed, to verify the quality of the sample preparation and the precision of the system. A daily QC is also conducted to verify that the system is working as expected. Both types of QC tests verify that the system's automatic detection process has properly detected the following:
   - The location of the particles by properly placing a bounding box around them.
   - Identification of megakaryocytes in the sample, without false detections.

V Standards/Guidance Documents Referenced:

- CLSI EP17-A2- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

- CLSI EP05-A3- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition
- CLSI EP12-A2- User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline – Second Edition
- ISO 15223-1 Fourth edition 2021-07; Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements
- ISO 7000 Sixth edition 2019-07; Graphical symbols for use on equipment – Registered symbols
- IEC 62366-1 Edition 1.1 2020-06 CONSOLIDATED VERSION Medical devices – Part 1: Application of usability engineering to medical devices
- ISO 14971: 2019; Medical devices – Applications of risk management to medical devices
- IEC 62304:2006/A1:2016; Medical device software – Software life cycle processes [Including Amendment 1 (2016)]
- IEC 60601-1-2:2014; 4th Edition: Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests
- IEC 62471 First edition 2006-07; Photobiological N/A safety of lamps and lamp systems
- IEC 61010-1 3rd Ed, dated May 12, 2012 with revision through July 19, 2019; Standard for Safety for Electrical Equipment For Measurement, Control and Laboratory Use; Part 1: General Requirements, FDA recognition number: 19-41
- IEC 61010-2-101: 2015, EN 61010-2-101:2017, Safety requirements for electrical equipment for measurement, control and laboratory use. Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment
- IEC 61010-1:2010/AMD1:2016, EN 61010-1:2010/A1:2019, Safety requirements for electrical equipment for measurement, control, and laboratory use – Part 1: General requirements

VI Performance Characteristics:

A Analytical Performance:

1) Precision

a) Repeatability: The study was conducted using one instrument (X100) at one site, with 12 Romanowsky stained slides (hereafter referred to as samples) that were randomly selected within the following three clinical groups: residual morphologic hematologic neoplasm (R), morphologic hematologic neoplasm (M), and normal morphology marrow (N). Samples were tested over 20 days with two runs per day, and two replicate scans for each run. In total, 960 scans were analyzed to evaluate repeatability, between-run, between-day, and within-laboratory precision using the device DSS pre-classified results without operator reclassification. The results met the pre-defined acceptance criteria.

Blasts

Sample	N	Mean (%)	Repeatability		Between-Run		Between-Day		Within-Laboratory	
			SD (%)	%CV	SD (%)	%CV	SD (%)	%CV	SD (%)	%CV
R1	80	9.43	0.69	7.28	0.59	6.26	0.00	0.00	0.91	9.60
R2	80	18.01	1.23	6.85	0.74	4.10	0.38	2.11	1.49	8.26
R3	80	8.04	0.78	9.75	1.32	16.4	0.00	0.00	1.54	19.11
R4	80	1.44	0.46	32.09	0.00	0.00	0.15	10.27	0.48	33.69
M1	80	64.78	1.84	2.83	0.58	0.89	0.51	0.79	1.99	3.07
M2	80	22.57	1.94	8.60	1.87	8.29	0.68	3.03	2.78	12.32
M3	80	6.79	0.67	9.81	0.35	5.15	0.00	0.00	0.75	11.08
M4	80	12.23	4.06	33.21	0.00	0.00	1.52	12.46	4.34	35.47
M5	80	7.92	1.42	17.94	0.57	7.15	0.35	4.42	1.57	19.81
M6	80	6.51	0.53	8.16	0.16	2.48	0.28	4.29	0.62	9.55
N1	80	4.35	0.36	8.38	0.33	7.57	0.00	0.00	0.49	11.30
N2	80	3.12	0.34	10.88	0.00	0.00	0.13	4.05	0.36	11.61

Plasma Cells

Sample	N	Mean (%)	Repeatability		Between-Run		Between-Day		Within-Laboratory	
			SD (%)	%CV	SD (%)	%CV	SD (%)	%CV	SD (%)	%CV
R1	80	3.80	0.34	9.01	0.25	6.69	0.11	2.91	0.44	11.60
R2	80	1.17	0.32	27.14	0.00	0.00	0.12	10.47	0.34	29.09
R3	80	2.94	0.53	17.93	0.32	11.07	0.18	6.19	0.64	21.96
R4	80	0.07	0.09	N/A	0.04	N/A	0.00	0.00	0.10	N/A
M1	80	4.94	0.94	19.04	0.94	18.96	0.00	0.00	1.33	26.87
M2	80	42.98	2.30	5.36	1.93	4.49	0.00	0.00	3.0	6.99
M3	80	0.24	0.07	N/A	0.00	0.00	0.03	N/A	0.08	N/A
M4	80	53.81	2.63	4.89	2.08	3.87	0.00	0.00	3.36	6.24
M5	80	24.48	3.39	13.86	0.00	0.00	2.39	9.77	4.15	16.95
M6	80	13.23	2.91	21.97	0.00	0.00	0.00	0.00	2.91	21.97
N1	80	1.05	0.27	25.35	0.14	13.67	0.04	3.96	0.30	29.07
N2	80	0.27	0.10	N/A	0.03	N/A	0.00	0.00	0.10	N/A

M:E Ratio

Specimen	Grade			True Grade	Agreement
	Normal	Abnormal	Too Few to Assess		
R1	80	0	0	Normal	100%
R2	0	80	0	Abnormal	100%
R3	3	77	0	Abnormal	96%
R4	0	80	0	Abnormal	100%
M1	0	80	0	Abnormal	100%
M2	0	4	76	Too Few to Assess	95%
M3	0	0	80	Too Few to Assess	100%

Specimen	Grade			True Grade	Agreement
	Normal	Abnormal	Too Few to Assess		
M4	0	0	80	Too Few to Assess	100%
M5	4	76	0	Abnormal	95%
M6	79	0	1	Normal	99%
N1	77	3	0	Normal	96%
N2	80	0	0	Normal	100%

a) Reproducibility: The study was conducted using nine Romanowsky stained slides randomly selected from the following three clinical groups: residual morphologic hematologic neoplasm (R), morphologic hematologic neoplasm (M), and normal morphology marrow (N), with three replicate scans for each slide. The study was performed at three sites with three runs per day over five days on four devices (three X100 and one X100HT) and four operators. In total, 540 scans were analyzed to evaluate repeatability, within-laboratory, between-day, between-site, and reproducibility using the DSS pre-classified results without operator reclassification. The results met the pre-defined acceptance criteria.

Blasts:

Sample	N	Mean Value (%)	Repeatability		Between-Day		Between-instrument/site		Reproducibility	
			SD (%)	%CV	SD (%)	%CV	SD (%)	%CV	SD (%)	%CV
R1	60	16.73	1.13	6.75	0.69	4.10	1.20	7.19	1.79	10.67
R2	60	8.41	1.30	15.50	0.93	11.05	1.61	19.14	2.27	26.99
R4	60	1.41	0.60	42.66	0.29	20.81	0.12	8.19	0.68	48.17
M1	60	61.02	1.94	3.18	0.81	1.33	4.06	6.65	4.57	7.49
M2	60	8.02	0.99	12.39	0.33	4.17	0.95	11.89	1.42	17.67
M4	60	11.64	2.47	21.24	1.12	9.59	0.00	0.00	2.71	23.30
M5	60	9.37	2.94	31.39	1.72	18.41	1.34	14.26	3.66	39.08
M6	60	6.51	0.58	8.86	0.10	1.55	0.00	0.00	0.59	8.99
N1	60	4.58	0.51	11.03	0.00	0.00	0.76	16.59	0.91	19.92

Plasma Cells:

Sample	N	Mean Value (%)	Repeatability		Between-Day		Between-Instrument/site		Reproducibility	
			SD (%)	%CV	SD (%)	%CV	SD (%)	%CV	SD (%)	%CV
R1	60	1.01	0.29	28.60	0.07	6.83	0.68	67.42	0.75	73.55

Sample	N	Mean Value (%)	Repeatability		Between-Day		Between-Instrument/site		Reproducibility	
			SD (%)	%CV	SD (%)	%CV	SD (%)	%CV	SD (%)	%CV
R2	60	2.71	0.81	29.80	0.92	33.99	2.03	74.89	2.37	87.47
R4	60	0.07	0.11	N/A	0.00	0.00	0.04	N/A	0.12	N/A
M1	60	3.76	0.72	19.03	0.31	8.30	2.90	77.06	3.00	79.81
M2	60	0.64	0.32	N/A	0.29	N/A	0.60	N/A	0.74	N/A
M4	60	49.56	5.35	10.79	2.92	5.90	0.89	1.79	6.16	12.43
M5	60	22.24	5.81	26.13	2.15	9.68	0.88	3.97	6.26	28.15
M6	60	13.80	2.45	17.72	1.67	12.09	0.84	6.07	3.08	22.29
N1	60	1.02	0.25	24.62	0.07	7.26	0.72	71.13	0.77	75.63

M:E Ratio

Specimen	Grade			True Grade	Agreement
	Normal	Abnormal	*Too Few to Assess		
R2	0	60	0	Abnormal	100%
R3	10	50	0	Abnormal	83%
R4	0	60	0	Increased	100%
M1	0	60	0	Abnormal	100%
M2	0	0	60	Too Few to Assess	100%
M4	0	3	57	Too Few to Assess	95%
M5	0	32	28	Increased	53%
M6	59	0	1	Normal	98%
N1	58	2	0	Normal	97%

*Too Few to Assess (TFTA): Insufficient information to determine a characteristic's grading

2) Linearity:

Not applicable

3) Analytical Specificity/Interference:

Not applicable

4) Assay Reportable Range:

Not applicable

5) Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Not applicable

6) Detection Limit:

Not applicable

7) Assay Cut-Off:

Not applicable

8) Accuracy (Instrument):

See Clinical studies section below.

9) Carry-Over:

Not applicable

B Comparison Studies:

1. Method Comparison:

See Clinical Study Section below.

2. Matrix Comparison:

Not applicable

C Clinical Studies:

1. Clinical Sensitivity and Specificity: The study was conducted at three sites with 615 Romanowsky stained slides. Manual microscopy was used as the reference method. The samples encompass multiple diseases that can be grouped into five clinical categories, as shown in the table below. The slides were randomly selected, blinded, and evaluated by two operators at each site. The operators were qualified to review bone marrow aspirates. The sample slides were evaluated by the test method and then by the reference method with a 3-week washout period in between. The DSS suggested results for the cell types/parameters were reviewed and confirmed or reclassified by the operators as necessary. The results met the pre-defined acceptance criteria.

Additional performance analysis was conducted for a subset of the 615 slides comparing the results of the candidate device with de-identified medical records data retrieved from two of the three sites.

Clinical conditions distribution:

Staining Method	Clinical Condition	Number of slides
Romanowsky Stain	Morphologic Hematologic neoplasm	180
	Residual morphologic hematologic neoplasm	180
	Benign	15
	Normal morphology marrow	180
	Others: Inadequate / Hemodiluted aspirate	60
Total		615

Romanowsky Stain:

1) Comparison of candidate device to manual microscopy

Specimen Quality Assessment

Qualitative analysis	Sensitivity (95%CI)	Specificity (95% CI)	Accuracy (95% CI)
Sample Quality (Adequate/Inadequate)	88.72% (82.22%, 93.05%)	99.36% (98.69%, 99.69%)	98.21% (97.31%, 98.82%)
Stripped Cells (Normal (<50%) / Increased)	66.67% (54.06%, 77.27%)	95.45% (94.07%, 96.52%)	93.99% (92.48%, 95.21%)
Semi-Quantitative analysis	**Sensitivity**	**Specificity**	**Agreement**
Sample quality (Particulate / Pauciparticulate / Aparticulate)	90.86% (86.02%, 94.14%)	99.42% (98.74%, 99.73%)	97.64% (96.63%, 98.35%)
Sample quality (Bloody tap / Diluted bone marrow / Adequate bone marrow)	91.88% (86.60%, 95.19%)	99.06% (98.29%, 99.49%)	96.25% (95.04%, 97.18%)

Count Estimation

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Blast Estimation (Normal (<5%/ Increased)	93.29% (89.96%, 95.57%)	87.39% (84.87%, 89.54%)	89.08% (87.09%, 90.80%)
Blast Estimation (<20% / >20%)	91.67% (87.21%, 94.66%)	96.34% (94.88%, 97.39%)	95.41% (94.00%, 96.50%)
Plasma Cell Estimation (<10% / ≥10%)	83.78% (75.82%, 89.49%)	97.65% (96.50%, 98.43%)	96.24% (94.94%, 97.22%)
M:E Ratio (Normal [2–4:1]+ Decreased / Increased)	89.74% (81.05%, 94.71%)	93.73% (91.74%, 95.27%)	93.35% (91.42%, 94.87%)
M:E Ratio (Normal [2–4:1] / Increased)	89.74% (81.05%, 94.71%)	84.92% (79.98%, 88.81%)	86.06% (81.91%, 89.38%)
M:E Ratio (Normal [2–4:1] / Decreased)	81.39% (77.30%, 84.89%)	75.09% (69.76%, 79.75%)	78.78% (75.57%, 81.67%)

2) Comparison of candidate device to de-identified medical data

	Positive percent agreement (PPA)	Negative Percent agreement (NPA)	Agreement
Blasts (<5% / Increased)	91.51% (87.47%, 94.32%)	89.43% (86.26%, 91.93%)	90.18% (87.78%, 92.16%)
Blasts (<20% / ≥20%)	89.42% (84.22%, 93.05%)	96.56% (94.64%, 97.82%)	94.67% (92.77%, 96.09%)
Plasma Cells (<10% / ≥10%)	89.19% (75.29%, 95.72%)	96.60% (94.95%, 97.72%)	96.21% (94.55%, 97.38%)
M:E Ratio (Normal [2–4:1] / Increased)	82.93% (68.74%, 91.48%)	79.12% (69.68%, 86.21%)	80.30% (72.70%, 86.19%)

2. Clinical Specificity:

Refer to Clinical Sensitivity

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The study was conducted to validate published reference ranges found in literature using 40 specimens collected from two sites. Samples were banked normal morphology BMA smears taken from U.S. individuals for which BMA has been deemed non-abnormal during routine lab evaluation. One Romanowsky stained BMA slide was obtained from each individual. Each sample was reviewed by two investigators (out of the four participating in the study), and the means of the two differential counts were used in the validation of the results. The differential count values were compared to the pre-defined reference intervals.

Parameter	**Range**
Blasts	0–5%[1]
Plasma Cells	0–7%[2]
M:E Ratio	2:1–4:1[3]

F Other Supportive Performance Characteristics Data:

1) Precision

a) Repeatability: The study was conducted using one instrument at one site, with 12 Romanowsky stain samples that were randomly selected from within three clinical groups (residual morphologic hematologic neoplasm (R), morphologic hematologic neoplasm (M), normal morphology marrow (N)). Samples were tested over 20 days with two runs/day, two replicate scans each. Precision was evaluated for eosinophils, basophils, mast cells, monocytes, lymphocytes, myeloid maturation which included promyelocytes, myelocytes, metamyelocytes, banded neutrophils, and segmented neutrophils, and erythroid maturation which included erythroblasts, basophilic normoblasts, polychromatophilic normoblasts, and normoblasts. Precision was found acceptable.

b) Reproducibility: The study was conducted using nine Romanowsky stain test samples randomly selected from three clinical groups (residual morphologic hematologic neoplasm (R), morphologic hematologic neoplasm (M), normal morphology marrow (N)) with three replicate scans. The study was performed at three sites with three runs/day over five days on four devices. Precision was evaluated for eosinophils, basophils, mast cells, monocytes, lymphocytes, myeloid maturation which included promyelocytes, myelocytes, metamyelocytes, banded neutrophils, and segmented neutrophils, and erythroid maturation which included erythroblasts, basophilic normoblasts, polychromatophilic normoblasts, and normoblasts. Precision was found acceptable.

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[1] M. E. Pollyea, "NCCN guidelines insights: acute myeloid leukemia, version 2.2021: featured updates to the NCCN guidelines," Journal of the National Comprehensive Cancer Network, vol. 19, no. 1, pp. 16-27, 2021.
[2] S. Parmentier et al., "Reevaluation of reference values for bone marrow differential counts in 236 healthy bone marrow donors," Ann Hematol, vol. 99, no. 12, pp. 2723- 2729, 2020.
[3] A. Orazi, D. P. O'Malley and D. A. Arber, "The normal bone marrow and an approach to bone marrow evaluation of neoplastic and proliferative processes," in Illustrated Pathology of the Bone Marrow, Cambridge, Cambridge University Press, 2006, pp. 5-15.

2) Clinical Sensitivity and Specificity: Assessment of the manually classified parameters were also conducted in the clinical study with three sites and 795 slides (615 Romanowsky stained, and 180 Prussian Blue stained). Manual microscopy was used as the reference method. The slides were randomly selected, blinded, and evaluated by two operators at each site. The sample slides were evaluated by the test method and then by the reference method with a 3-week washout period in between. The images were reviewed and cell types were classified by the operators. For Romanowsky stained BMA smears, count estimation was assessed for basophils, eosinophils, lymphocytes, megakaryocytes, monocytes, and mast cells while Maturation and Morphology was assessed for blast auer rods detections, blast nucleus morphology, blast granulation detections, erythropoiesis maturation, erythropoiesis morphology, myelopoiesis maturation, myelopoiesis morphology, lymphocyte morphology, megakaryocytes maturation, megakaryocytes morphology, monocyte morphology, and plasma cell morphology. For Prussian blue stained BMA smears, iron specimen quality, iron stores, and ring sideroblasts detections were assessed. The results demonstrated that the images provided for manual determination of the cell categories was appropriate.

Clinical conditions distribution:

Staining Method	**Clinical Condition**	**Number of slides**
Romanowsky Stain	Morphologic Hematologic neoplasm	180
	Residual morphologic hematologic neoplasm	180
	Benign	15
	Normal morphology marrow	180
	Others: Inadequate / Hemodiluted aspirate	60
Prussian Blue Stain	Others: Evaluation of Iron Stores	180
Total		795

3) **Too Few to Assess (TFTA) Grading:** TFTA grading was used when an investigator identified that they did not have enough information to determine a characteristic's grading. During the Clinical Study, the users performed the same evaluation with regards to TFTA for both manual microscopy and Full Field BMA device. The criteria indicated below were used to assess TFTA. In total, out of 7,662 cases that were assessed using the manual microscope as TFTA, 94.53% were also assessed using Scopio Labs Full Field BMA as too few to assess.

Criteria for TFTA Evaluation

Cell	Evaluation parameter	Prerequisite for determination	TFTA Criteria
Erythropoiesis	**Maturation**	Presence of Erythroid cells	Less than 50 Erythroid cells are detected
	Morphology	Presence of abnormal Erythroid cells	Less than 50 Erythroid cells are detected
M:E Ratio	**Estimation**	Presence of Myeloid and Erythroid cells	Total count of Myeloid and Erythroid out of the total number of cells is less than 50%
Megakaryocytes	**Maturation**	Determination by Megakaryocytes cells size	Less than 30 Megakaryocytes are detected
	Morphology	Presence of abnormal Megakaryocytes, marked manually by the users as abnormal during the review process	Less than 30 Megakaryocytes are detected
Monocytes	**Morphology**	Presence of abnormal Monocytes, marked manually by the users as abnormal during the review process	Less than 20 Monocytes are detected
Myelopoiesis	**Maturation**	Presence of Myeloid cells	Less than 50 Myeloid cells are detected
	Morphology	Presence of abnormal Myeloid cells marked manually by the users as abnormal during the review process	Less than 50 Myeloid cells are detected

4) **Inadequate Samples Quality**: The number of samples for which users chose 'inadequate' in the Sample Quality primary characteristic in each of the methods was compared. Users marked 1,450 cases as adequate using Scopio Labs Full Field BMA, and in 98.76% of the times they were also marked as adequate when using the manual microscope.

5) **Scanning Area Performance**: The comparison used the percentage (%) of the combined particle areas falling within the suggested scan area as a metric. An overall score was defined as the average score of all Romanowsky stained cases which were not characterized by the user as "Inadequate" or "Aparticulate" using the reference method. An overall score of 91.10% was obtained.

6) **Inter-User Agreement**: Samples were reviewed separately by each of the two users at the sites. Each of the user's results in the test method were compared to the same user's results in the reference method. Agreement between the two users' results when using a manual

microscope was calculated, and the agreement between the two users' results when using the test method.

VII Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

VIII Identified Risks and Mitigations:

Risks to Health	Mitigation Measures
Clinical action based on false positive results may lead to misdiagnosis, inappropriate patient management, or unnecessary treatments.	Certain design verification and validation, including documentation of certain analytical studies and clinical studies. Certain labeling information, including limitations.
Clinical action based on false negative results may lead to delayed diagnosis, missed diagnosis, or delay in treatment.	Certain design verification and validation, including documentation of certain analytical studies and clinical studies. Certain labeling information, including limitations.

IX Benefit/Risk Assessment:

A Summary of the Assessment of Benefit:

There is currently no FDA authorized automated cell locating device for evaluating cell types in bone marrow aspirates (BMA). Currently, to perform analysis of BMA smears, laboratories use manual microscopy, or a camera mounted on a manual microscope to perform 500–1000 nucleated cell differentials at 100x resolution. The X100 and X100HT instruments with software application (Full Field BMA Application) is intended to perform the same functions in a digital workflow. The Full Field BMA application can provide the intended users with pre-classification results for slide quality, blasts, plasma cells and M/E ratio. The level of blasts in bone marrow is particularly important. Having at least 20% blasts in the bone marrow is required for the diagnosis of acute myeloid leukemia. Blast count of 5% is an important diagnostic threshold for the sub-classification of myelodysplastic syndrome. In patients with multiple myeloma, abnormal clonal plasma cells make up at least 10% of the cells in the bone marrow. M:E ratio compares the relative numbers of myeloid precursors to erythroid precursors. Together with overall bone marrow cellularity, M:E ratio helps assess changes in the myeloid and erythroid cell populations. The Full Field BMA application can generate qualitative or semiquantitative pre-classification results based on clinically relevant medical decision levels (e.g., 5% and 20% for blasts). Comparing to manual smear review, the device shows favorable sensitivities in detecting samples with abnormally increased cell counts. The performances for analytical validations of

these parameters are acceptable. The probable benefits of the pre-classification functions include facilitating more effective BMA assessment and reducing potential user errors such as underestimating blast counts.

B Summary of the Assessment of Risk:

The risks of the device include false negative or false positive results due to incorrect suggestions offered to the user by the system's DSS (Decision Support System) in the scanning and/or analysis stages. This risk can occur in the selection of the scanned area (the user may not see all the relevant areas in the slide), in the selection of optimal NDC-ROI (region of interest for nucleated differential count) where the user may not review all the relevant cells, and in the cells' pre-classification stage (which can lead to inaccurate lineage assessment being presented to the user). Incorrect suggestions offered by the system may lead to delayed diagnosis, missed diagnosis, or delay in treatment.

C Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

D Summary of the Assessment of Benefit-Risk:

There is probable risk associated with an erroneous result. To mitigate the risks, analytical and clinical studies are performed for verification and validation. Labeling information, including limitations and user training are included such as the labeling clearly states that the user must verify and revise the suggested results as needed. The intended users of the device are qualified in BMA assessment, who have the expertise to evaluate the system's DSS suggestions. The risk mitigation strategies and special controls are sufficient to mitigate the risks. While general controls are not sufficient to mitigate the risks, in light of the special controls, the benefits of the device outweigh the risks.

X Conclusion:

The De Novo request is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): SAL
Device Type: Automated cell-locating device for bone marrow aspirate
Class: II
Regulation: 21 CFR 864.5261