Luminex

White Paper

Introducing Sheath Fluid PLUS and Drive Fluid PLUS for xMAP® Systems

General Information

Summary of Change

Luminex has developed a new PLUS formulation for the xMAP® Sheath Fluid and MAGPIX® Drive Fluid products. The formulation has been updated to replace one mode of antimicrobial action (ProClin™) with three modes of antimicrobial action (sodium azide, sodium benzoate, and diazolidinyl urea). This new design offers greater transit stability, and helps avoid potential compromises in preservative potency or discoloration associated with ProClin™ degradation. Further, this updated antimicrobial cocktail provides enhanced protection for the system fluidic pathway, and addresses the prevalence of environmental microbial resistance to ProClin™. The new PLUS formulation will be sold under new part numbers and product names, as shown in **Table 1**.

New Formulation

The current formulation contains a single bacteriostatic preservative, ProClin™, which is susceptible to microbial resistance and degradation following prolonged heat exposure. The new PLUS formulation contains sodium azide (a bacteriostatic), sodium benzoate (a bacteriostatic and fungistatic), and diazolidinyl urea (a broad-spectrum bacteriostatic and bactericidal), which, when combined, provide a greater range of antimicrobial effectiveness compared to ProClin™ alone, and are better suited for prolonged exposure to ambient temperature during transport. The core formulation of the sheath fluid is unchanged—it is still a dilute PBS solution comprised of 99% water and 1% of the following: sodium/potassium salts, phosphate salts, sodium azide, sodium benzoate, and diazolidinyl urea.

New Part Numbers

While the formulations between the RUO and IVD labeled versions do not differ, it is important to make sure the appropriately labeled product for your intended use is utilized.

Table 1. Sheath Fluid PLUS and Drive Fluid PLUS Part Numbers

Current Part Number	Current Product Name	New Part Number	New Product Name
40-50015	xMAP® Sheath Fluid, 20 L, RUO	40-50021	xMAP® Sheath Fluid PLUS, 20 L, RUO
40-50000	xMAP® Sheath Fluid, 20 L (IVD)	40-50035	xMAP® Sheath Fluid PLUS, 20 L, IVD
MPXDF-4PK	MAGPIX® Drive Fluid, 4 Pack (RUO)	40-50030	MAGPIX® Drive Fluid PLUS, 4PK, RUO
MPXDF-4PK-1	MAGPIX® Drive Fluid, 4 Pack, EU IVD	40-50020	MAGPIX® Drive Fluid PLUS, 4PK, IVD
40-50014*	MAGPIX® Drive Fluid System, 2 Pack	40-50022*	MAGPIX® Drive Fluid PLUS, System, 2 pack
40-50013†	MAGPIX® Drive Fluid, 700 mL	40-50019†	MAGPIX® Drive Fluid PLUS, 700 mL

*System 2 Pack included with new MAGPIX® instrument purchase. Not available for individual sale.

†700 mL bottles included in 2 Pack and 4 Pack. Not available for individual sale.

Release Specifications

The PLUS formulation will have similar release specifications compared to the current ProClin™ formulation, as shown in **Table 2**.

Table 2. Comparison of ProClin™ Sheath Fluid and Drive Fluid to Sheath Fluid PLUS and Drive Fluid PLUS Formulation

	ProClin™ Sheath and Drive Fluid	Sheath Fluid PLUS and Drive Fluid PLUS
pH	7.30–7.50	7.30–7.50
Conductivity (mS)	16.0–18.0	15.0–17.0
Refractive Index	1.3344–1.3354	1.3344–1.3354
Bioburden	<20 cfu/L per 50 mL sample	<20 cfu/L per 50 mL sample

Transitioning to PLUS Formulation

Although it is not required, users can flush the ProClin™ formulation out of the system before implementing the use of the PLUS formulation. For detailed instructions, refer to the **Sheath and Drive Fluid Flush Procedure**.

Stability Study of Sheath Fluid PLUS and Drive Fluid PLUS

Overview

The stability study consisted of testing material in an accelerated format while also evaluating the PLUS formulation under heat stress and freeze/thaw cycles for a duration of time to substantiate a real-time equivalent of 1-year shelf life at the time of RUO release. After subsequent testing, we determined the new PLUS formulation has a 2-year shelf life from the date of manufacture. All lots manufactured after August 2020 are shelf-stable for 2 years.

For accelerated testing, all samples were stored in primary product containers at 45°C (42–48°C). Accelerated samples were pulled and tested at 0.5, 1.0, 1.2, 1.7, and 2.2 years to confirm shelf-life dating. This accelerated study also served as a heat stress study, given the temperature and duration evaluated. For the freeze/thaw study, lots underwent two freeze/thaw cycles and were then accelerated at 45°C to confirm a 2.2 year shelf-life.

Table 3. Test Parameters and Measurement Methods

Test Parameter and/or Critical Attributes	Method
pH	pH meter
Conductivity	Conductivity meter
Refractive Index (RI)	Refractometer
Aerobic Bioburden	Internal bioburden testing method
Antimicrobial Effectiveness Testing	Challenge testing per United States Pharmacopeia, 28th revision, chapter 51. Results will be analyzed per a log reduction evaluation.
Visual Inspection	Visual inspection per internal attribute inspection SOP
Luminex® 100/200™ Performance Evaluation	xMAP® Sheath Fluid PLUS only. Luminex® 100/200™ was drained and primed with the 40-50035 test lots and the system was recalibrated. L100-CON1 and L100-CON2 verifier reagent values were used to evaluate reagent system performance.
FLEXMAP 3D® Performance Evaluation	xMAP® Sheath Fluid PLUS only. FLEXMAP 3D® was drained and primed with the 40-50035 test lots and the system was recalibrated. F3DVER1-05 and F3DVER2-05 verifier reagent values were used to evaluate reagent system performance.
MAGPIX® Performance Evaluation	MAGPIX® Drive Fluid PLUS only. MAGPIX® System was drained and primed with 40-50019 test lots and the system was recalibrated. MPXVER-05 values were used to evaluate reagent system performance.

Table 4. Sheath Fluid PLUS Results

Attribute	Specification	Pass/Fail
pH	7.0–7.5*	Pass
Conductivity	13.0–18.0 mS	Pass
Refractive Index (RI)	1.3340–1.3360	Pass
Aerobic Bioburden	<20 cfu/L	Pass
Antimicrobial Effectiveness Testing	Per USP <51> Category 2, for bacteria, not less than a 2.0 log reduction from the initial count at 14 days, and no increase from the 14 day count at 28 days. For yeast and molds, no increase from the initial calculated count at 14 and 28 days.	Pass
Visual Inspection	Clear, colorless liquid using visual inspection, per internal attribute inspection SOP.	Pass
Luminex® 100/200™ Performance Evaluation	Instrument was able to successfully complete calibration and verification.	Pass
FLEXMAP 3D® Performance Evaluation	Instrument was able to successfully complete calibration and verification.	Pass

*See Additional Notes.

Table 5. Drive Fluid PLUS Results

Attribute	Specification	Pass/Fail
pH	7.0–7.5*	Pass
Conductivity	13.0–18.0 mS	Pass
Refractive Index (RI)	1.3340–1.3360	Pass
Aerobic Bioburden	<20 cfu/L	Pass
Antimicrobial Effectiveness Testing	Per USP <51> Category 2, for bacteria, not less than 2.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days. For yeast and molds, no increase from the initial calculated count at 14 and 28 days.	Pass
Visual Inspection	Clear, colorless liquid using visual inspection as per internal Attribute Inspection SOP.	Pass
MAGPIX® Performance Evaluation	Instrument was able to successfully complete calibration and verification.	Pass

*See Additional Notes.

Additional Notes

*Initially, the pH stability specification for Sheath Fluid PLUS was 7.3–7.5, which was derived from the release specification of 7.30–7.50. However, the stability study results showed that the pH range fell from 7.4 to 7.2 over a 1-year equivalent timeframe, and these results prompted further investigation into the requirement range. The intent of the pH requirement for Sheath Fluid and Sheath Fluid PLUS is to ensure compatibility with bioassays. The pH requirement for the original Sheath Fluid formulation was "pH shall be compatible with bioassays, i.e., greater than 7.0". Therefore, the lower end of the original pH requirement (pH 7.0) was evaluated in the context of bioassay verification. Assay compatibility testing was performed on multiple sheath formulations, including an aged Sheath Fluid PLUS formulation adjusted to pH 7.05. Please refer to the Assay Compatibility section of this document for the results of this testing. Having met the intent of the pH requirement, the stability specification was changed to 7.0–7.5. The Sheath Fluid PLUS release specification remains pH 7.30–7.50.

Antimicrobial Effectiveness testing was performed by the MicroChem Laboratory per the criteria defined in the United States Pharmacopeia (USP) Chapter 51, Category 2 Preservative Challenge Test (28th revision). Much like a Preservative Challenge Screen, this test is a common method used to gauge preservative effectiveness in cosmetics, personal care products, and drug products. USP success is defined by a ≥2.0 log10 cfu/mL reduction in the initial inoculum at 14 days, and no increase from the 14 day viability sampling interval count at 28 days per substance. Five prescribed microorganisms and four environmental isolates derived from ProClin™-resistant microorganisms were spiked into all lots tested per USP <51> guidelines. See **Table 6** for a list of microorganisms used in this testing.

Table 6. Microorganisms Examined for Antimicrobial Effectiveness Testing

Microbe	Type
Pseudomonas aeruginosa	Bacterial
Staphylococcus aureus	Bacterial
Escherichia coli	Bacterial
Candida albicans	Fungal
Aspergillus brasiliensis	Fungal
Burkholderia cepacia complex*	Bacterial
*Microbacterium liquefaciens**	Bacterial
*Microbacterium maritypicum**	Bacterial
*Microbacterium oxydans**	Bacterial

*Microbes found in environmental isolates.

Assay Compatibility Testing

Assay compatibility testing does not replace the need for specific assay validation activities. This testing intended to demonstrate that the PLUS formulation is compatible with a range of assay chemistries and does not cause any adverse effects (such as unwinding DNA duplexes, quenching reporter dye fluorescence, or breaking up antigen-antibody interactions). The testing does not indicate how well the assay ran, or compare the ProClin™ formulation to the PLUS; instead, it demonstrates that the assay returned the expected result regardless of the type of Sheath Fluid used.

Materials and Methods

Three assays were used for testing:

1. Bio-Techne Human XL Cytokine Discovery Panel (Catalog # FCSTM18), 2-plex with IL-6 and TNF-alpha
    a. Available for use on the MAGPIX®, Luminex® 200™, and FLEXMAP 3D®.
2. Luminex NxTAG® Respiratory Pathogen Panel (RPP) CE-IVD (Catalog # 1051C0447)
    a. Available for use on the MAGPIX only.
3. Luminex xTAG® Gastrointestinal Pathogen Panel (GPP) CE-IVD (Catalog # 1032C0316)
    a. Available for use on the Luminex 200.

These three assays were first tested using the legacy Sheath ProClin™ formulation as a control to show that the kit performed as expected. The assays were then repeated using the following Sheath Fluid PLUS or Drive Fluid PLUS configurations to verify that the results were comparable and within the expected range.

1. <1 month room temperature aged, no pH adjustment (pH 7.40)

2. Pulled from accelerated 45ºC storage, no pH adjustment (equivalent to 2-year shelf-life, pH 7.20)

3. Pulled from accelerated 45ºC storage, pH adjusted (equivalent to 2-year shelf-life, pH 7.05)

Results are summarized for each instrument in **Table 7**.

Results

Luminex® 200™

Table 7. Luminex® 200™ Assay Compatibility Testing Performance

Assay	Sheath Fluid Type	Specification	Pass/Fail
Bio-Techne Cytokine	RT ProClin™	A standard curve with 1 blank and 7 concentrations of analytes in 3-fold serial dilution will be compared for matching results of the standards between ProClin™ Sheath and Sheath Fluid PLUS. The test results from ProClin™ Sheath should be used as reference concentrations. For a "pass," test results from Sheath Fluid PLUS must fall within 20% of the ProClin™ Sheath and the readings for the two cytokine antigens in the kit should fall within 25% for the high concentration and 35% for the low concentration of each antigen.	Pass
	RT PLUS		Pass
	Aged (at 45°C) PLUS		Pass
	Aged (at 45°C) pH 7.05 PLUS		Pass
Luminex xTAG® GPP	RT ProClin™	Wells with adenovirus type 40 DNA plus MS2 will return a positive test result for adenovirus and MS2 internal controls. All other targets will return negative results.	Pass
	RT PLUS		Pass
	Aged (at 45°C) PLUS		Pass
	Aged (at 45°C) pH 7.05 PLUS		Pass

FLEXMAP 3D®

Table 8. FLEXMAP 3D® Assay Compatibility Testing Performance

Assay	Sheath Fluid Type	Specification	Pass/Fail
Bio-Techne Cytokine	RT ProClin™	A standard curve with 1 blank and 7 concentrations of analytes in 3-fold serial dilution will be compared for matching results of the standards between ProClin™ Sheath and Sheath Fluid PLUS. The test results from ProClin™ Sheath will be used as reference concentrations. For a "pass," test results from Sheath Fluid PLUS should fall within 20% of the ProClin™ Sheath, and the readings for the two cytokine antigens should fall within 25% for the high concentration and 35% for the low concentration of each antigen.	Pass
	RT PLUS		Pass
	Aged (at 45°C) PLUS		Pass
	Aged (at 45°C) pH 7.05 PLUS		Pass
Luminex xTAG® GPP	RT ProClin™	Wells with adenovirus type 40 DNA plus MS2 will return a positive test result for adenovirus and MS2 internal controls. All other targets will return negative results.	Pass
	RT PLUS		Pass
	Aged (at 45°C) PLUS		Pass
	Aged (at 45°C) pH 7.05 PLUS		Pass

MAGPIX®

Table 9. MAGPIX® Assay Compatibility Testing Performance

Assay	Drive Fluid Type	Specification	Pass/Fail
Bio-Techne Cytokine	RT ProClin™	A standard curve with 1 blank and 7 concentrations of analytes in 3-fold serial dilution will be compared for matching results of the standards between ProClin™ Drive Fluid and Drive Fluid PLUS. The test results from ProClin™ Drive Fluid will be used as reference concentrations. For a "pass," test results from Drive Fluid PLUS should fall within 20% of the ProClin™ Drive Fluid, and the readings for the two cytokine antigens kit should fall within 25% for the high concentration and 35% for the low concentration of each antigen.	Pass
	RT PLUS		Pass
	Aged (at 45°C) PLUS		Pass
	Aged (at 45°C) pH 7.05 PLUS		Pass
Luminex NxTAG® RPP	RT ProClin™	Wells with adenovirus type 40 DNA plus MS2 will return a positive test result for adenovirus and MS2 internal controls. All other targets will return negative results.	Pass
	RT PLUS		Pass
	Aged (at 45°C) PLUS		Pass
	Aged (at 45°C) pH 7.05 PLUS		Pass

Table 10. Material Compatibility Testing

Material Tested	Procedure	Passing Criteria	Result
Exterior components	A paper towel saturated with Sheath Fluid PLUS was rubbed on the various surfaces of xMAP® Instruments for 20 seconds 5 times and exterior components were inspected for degradation.	No crazing, cracking, softening, or swelling of components after exposure to sheath fluid.	Pass
Interior components	All components that are in common contact with Sheath/Drive Fluid were placed in 50 mL Falcon® tubes, soaked for 30 days, and then visually inspected for degradation.	No crazing, cracking, softening, or swelling of components after exposure to sheath fluid.	Pass
Instrument labels	One of each type of label was affixed to an Luminex® 200™ back-plate. A Sheath Fluid PLUS-saturated paper towel was rubbed on each label for 20 seconds 5 times. The labels were then visually inspected.	Labels must adhere and remain legible following exposure to sheath fluid.	Pass
Reagent labels	One of each of type of label was affixed to its appropriate container. Sheath Fluid PLUS was sprayed on each label and allowed to dry 5 times. The labels were then visually inspected.	Labels must adhere and remain legible following exposure to sheath fluid.	Pass

Conclusion

The verification and validation plans outlined the use of specific methods, procedures, acceptance criteria, and statistical techniques with rationale for sample size in compliance with the ISO 13485 Standard. The execution of the verification and validation plans demonstrated the ability of these processes to achieve planned results consistently. As all acceptance criteria outlined within the plans were met for xMAP Sheath Fluid PLUS and MAGPIX Drive Fluid PLUS, these products are considered validated.

Manufacturer's Declarations

1. These products do not contain any viruses, bacteria, or any other microorganisms.

2. These products do not contain any antigens derived from viruses, bacteria, or any other microorganisms.

3. These products do not test for antibodies raised against viruses, bacteria, or any other microorganisms.

4. These products do not contain any animal, human, plant, fungi, algae, or disease agent derived ingredients and no such ingredients were used in the manufacture of the products.

5. These products are not intended for human body application or consumption.

6. These products contain less than 0.025% sodium azide.

7. These products are non-hazardous, non-infectious, and non-toxic.

8. Type of packaging

    a. xMAP® Sheath Fluid PLUS (40-50021 and 40-50035)

        i. Square corrugate box with 20L in plastic capped bladder (cubitainer) [Note: a container rated at UN 4G/Y32/S/18 may be used for shipping durability purposes, formulation is non-hazardous, refer to product SDS].

    b. MAGPIX® Drive Fluid PLUS, 4 Pack (40-50030 and 40-50020)

        i. Corrugate box with 4 x 700 mL in HDPE induction sealed bottle.

    c. MAGPIX® Drive Fluid PLUS, 2 Pack (40-50022)

        i. Corrugate box with 2 x 700 mL in HDPE induction sealed bottle.

9. Volume of each item

a. 40-50021	xMAP® Sheath Fluid PLUS, 20 L, RUO	20 L
b. 40-50035	xMAP® Sheath Fluid PLUS, 20 L, IVD	20 L
c. 40-50030	MAGPIX® Drive Fluid PLUS, 4PK, RUO	4 x 700 mL
d. 40-50020	MAGPIX® Drive Fluid PLUS, 4PK, IVD	4 x 700 mL
e. 40-50022	MAGPIX® Drive Fluid PLUS System 2 Pack	2 x 700 mL
f. 40-50019	MAGPIX® Drive Fluid PLUS, 700 mL	700 mL

10. Intended use

    a. Use xMAP® Sheath Fluid PLUS (40-50021, 40-50035) as the delivery medium, which carries the sample to the optics component of xMAP® Technology-based instruments.

    b. Use MAGPIX® Drive Fluid PLUS (40-50030, 40-50020, 40-50022, 40-50019) as the delivery and flush medium, which carries the sample to the optics component of MAGPIX-based instruments.

Table 11. Additional Documents*

Document Type	Document Number	Document Name
Product Information Sheet	89-60000-00-179	Product Information Sheet, MAGPIX® Drive Fluid PLUS 4 Pack RUO, English
Product Information Sheet	89-60000-00-173	Product Information Sheet, MAGPIX® Drive Fluid PLUS 4 Pack IVD, English
Product Information Sheet	89-60000-00-153	Product Information Sheet, MAGPIX® Drive Fluid PLUS System 2 Pack, English
Product Information Sheet	89-60000-00-177	Product Information Sheet, xMAP® Sheath Fluid PLUS 20L RUO, English
Product Information Sheet	89-60000-00-174	Product Information Sheet, xMAP® Sheath Fluid PLUS 20L IVD, English
Safety Data Sheet (SDS)	89-40000-00-948	SDS, xMAP® Sheath Fluid PLUS
Safety Data Sheet (SDS)	89-40000-00-949	SDS, MAGPIX® Drive Fluid PLUS
Customer Instructions	N/A	**Sheath and Drive Fluid Flush Procedure**

*For SDS and IVD product information sheet translations, please visit luminexcorp.com/documents.

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