Introducing Sheath Concentrate PLUS for xMAP® Systems

General Information

Summary of Change

Luminex has developed a new PLUS formulation for the xMAP® Sheath Concentrate Pack. 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**.

In addition to the change in formulation, there is also a minor change in packaging. Instead of storing the preservative in a separate vial from the 1L concentrate, as found in the current configuration, the preservative cocktail is already mixed in with the contents of the 1L bottle. Due to this change, the outer cardboard box for xMAP® Sheath Concentrate PLUS is 3 in (7.6 cm) shorter (see **Table 2** for outer box measurements).

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 PLUS formulation of Sheath Concentrate contains 80% water and 20% of the following components:

- Sodium/potassium salts
- Phosphate salts
- Sodium azide
- Sodium benzoate
- 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 Concentrate PLUS Part Numbers

Current Part Number	Current Product Name	New Part Number	New Product Name
40-50018	xMAP® Sheath Concentrate Pack, RUO	40-50023	xMAP® Sheath Concentrate PLUS, RUO
40-75680	Sheath Concentrate Pack (IVD)	40-50036	xMAP® Sheath Concentrate PLUS, IVD

Release Specifications

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

Table 2. Formulation and Packaging: Comparison of ProClin™ Sheath Concentrate to Sheath Concentrate PLUS

	ProClin™ Sheath Concentrate	Sheath Concentrate PLUS
pH	6.45–6.70	6.1–6.7
Conductivity (mS)	165–186	165–186
Refractive Index	1.3469–1.3741	1.3469–1.3741
Bioburden	<20 cfu/L per 50 mL sample	<20 cfu/L per 50 mL sample
Outer Box Dimensions	4 in. x 4 in. x 12 in. (10 cm x 10 cm x 30.5 cm)	4 in. x 4 in. x 9 in. (10 cm x 10 cm x 22.7 cm)

Transitioning to the 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**.

Note: *xMAP® Sheath Concentrate PLUS must be diluted per instructions on the Product Information Sheet before using.*

Stability Study of xMAP® Sheath Concentrate PLUS

Overview

The stability study consisted of testing undiluted material in an accelerated format while also evaluating the product 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. Subsequent testing was performed on material diluted to the 1X working concentration to substantiate an additional 3 months of shelf life once diluted. Additional testing will be performed with the goal of extending the shelf life.

For accelerated (Acc) testing, test articles were kept in primary product containers at 45°C (42–48°C), and time points were selected to substantiate 0.8 and 1.1 years. The Acc study also served as a heat stress study, given the temperature and duration evaluated. For the freeze/thaw study, lots were subjected to 3 freeze/thaw cycles and were then placed in 45°C incubators for Acc aging, and a time point was selected to substantiate 1.1 years. At the equivalent age of 1.1 years, heat stressed and freeze thawed samples were diluted volumetrically to the 1X working concentration and placed in Acc 45°C storage to substantiate an additional 3.1 months of shelf life after dilution.

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 as per a log reduction evaluation. Instructions included in detailed stability protocol.
Visual Inspection	Visual inspection per internal attribute inspection SOP
Luminex® 100/200™ Performance Evaluation*	xMAP® Sheath Concentrate PLUS (13-90005†) was diluted to the 1X working concentration. The Luminex® 100/200™ System was drained and primed with the 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 Concentrate PLUS (13-90005) was diluted to the 1X working concentration. The FLEXMAP 3D® System was drained and primed with the test lots and the system was recalibrated. F3DVER1-05 and F3DVER2-05 verifier reagent values were used to evaluate reagent system performance.

**Testing only performed on aged, diluted xMAP® Sheath Concentrate PLUS.*

†13-90005 is the reagent component of 40-50023 and 40-50036 and is not available for individual purchase. This component carries no regulatory designation.

Table 4. Undiluted xMAP® Sheath Concentrate PLUS Results

Attribute	Specification	Pass/Fail
pH	6.1–6.7	Pass
Conductivity	165–186	Pass
Refractive Index (RI)	1.3469–1.3741	Pass
Aerobic Bioburden	<20 cfu/L	Pass
Visual Inspection	Clear, colorless liquid using visual inspection, per internal attribute inspection SOP.	Pass

Table 5. Aged, Diluted xMAP® Sheath Concentrate 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.*

*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, we evaluated the lower end of the original pH requirement (pH 7.0) 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 **Introducing Sheath Fluid PLUS and Drive Fluid PLUS for xMAP® Systems** 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 MicroChem Laboratory as 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 $\log^{10}$ cfu/L 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 were spiked into all lots tested per USP <51> guidelines, as well as into environmental isolates derived from ProClin™-resistant microorganisms. 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 is 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.

Assay compatibility testing was not performed with diluted xMAP® Sheath Concentrate PLUS because xMAP® Sheath Fluid PLUS and diluted xMAP® Sheath Concentrate PLUS are the same reagent with the same ingredients, concentrations and chemical properties. While the testing was only conducted with xMAP® Sheath Fluid PLUS, any requirements specifying diluted xMAP® Sheath Concentrate PLUS will be deemed to be equally verified. Refer to **Introducing Sheath Fluid PLUS and Drive Fluid PLUS for xMAP® Systems** for the results of assay compatibility testing with xMAP® Sheath Fluid PLUS.

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 Concentrate PLUS, this product is 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 0.45% sodium azide.
7. These products are non-hazardous, non-infectious, and non-toxic.
8. Type of Packaging for xMAP® Sheath Concentrate PLUS (40-50023 and 40-50036)
    a. Corrugate box with 1L in PPCO bottle and polypropylene screw cap closure.
9. Volume of Each Item
    a. 40-50023 xMAP® Sheath Concentrate PLUS, 20L, RUO 1L.
    b. 40-50036 xMAP® Sheath Concentrate PLUS, 20L, IVD 1L.
10. Intended use
    a. Use diluted xMAP® Sheath Concentrate PLUS (40-50023, 40-50036) as the delivery medium, which carries the sample to the optics component of xMAP® Technology-based instruments.

Table 11. Additional Documents*

Document Type	Document Number	Document Name
Product Information Sheet	89-60000-00-178	Product Information Sheet, xMAP® Sheath Concentrate PLUS (1L) (RUO), English
Product Information Sheet	89-60000-00-176	Product Information Sheet, xMAP® Sheath Concentrate PLUS (1L) (IVD), English
Safety Data Sheet	89-40001-00-199	SDS, xMAP® Sheath Fluid Concentrate PLUS, US English
Safety Data Sheet	89-40001-00-385	SDS, xMAP® Sheath Fluid Concentrate PLUS, English (Australia)
Safety Data Sheet	89-40001-00-386	SDS, xMAP® Sheath Fluid Concentrate PLUS, English (N. Zealand)
Safety Data Sheet	89-40001-00-387	SDS, xMAP® Sheath Fluid Concentrate PLUS, Chinese (China)
Safety Data Sheet	89-40001-00-388	SDS, xMAP® Sheath Fluid Concentrate PLUS, English (India)
Safety Data Sheet	89-40001-00-389	SDS, xMAP® Sheath Fluid Concentrate PLUS, English (Singapore)
Safety Data Sheet	89-40001-00-390	SDS, xMAP® Sheath Fluid Concentrate PLUS, Dutch (Netherlands)
Safety Data Sheet	89-40001-00-391	SDS, xMAP® Sheath Fluid Concentrate PLUS, French (Canada)
Safety Data Sheet	89-40001-00-392	SDS, xMAP® Sheath Fluid Concentrate PLUS, Italian (Italy)
Safety Data Sheet	89-40001-00-393	SDS, xMAP® Sheath Fluid Concentrate PLUS, German (Germany)
Safety Data Sheet	89-40001-00-394	SDS, xMAP® Sheath Fluid Concentrate PLUS, Chinese (Taiwan)

Table 11. Additional Documents*

Document Type	Document Number	Document Name
Safety Data Sheet	89-40001-00-395	SDS, xMAP® Sheath Fluid Concentrate PLUS, Japanese (Japan)
Safety Data Sheet	89-40001-00-396	SDS, xMAP® Sheath Fluid Concentrate PLUS, French (France)
Safety Data Sheet	89-40001-00-397	SDS, xMAP® Sheath Fluid Concentrate PLUS, English (Great Britain)
Safety Data Sheet	89-40001-00-398	SDS, xMAP® Sheath Fluid Concentrate PLUS, German (Austria)
Safety Data Sheet	89-40001-00-399	SDS, xMAP® Sheath Fluid Concentrate PLUS, Swedish (Sweden)
Safety Data Sheet	89-40001-00-400	SDS, xMAP® Sheath Fluid Concentrate PLUS, Russian (Russia)
Safety Data Sheet	89-40001-00-401	SDS, xMAP® Sheath Fluid Concentrate PLUS, German (Switzerland)
Safety Data Sheet	89-40001-00-402	SDS, xMAP® Sheath Fluid Concentrate PLUS, Indonesian (Indonesia)
Safety Data Sheet	89-40001-00-403	SDS, xMAP® Sheath Fluid Concentrate PLUS, Estonian (Estonia)
Safety Data Sheet	89-40001-00-404	SDS, xMAP® Sheath Fluid Concentrate PLUS, English (Ireland)
Safety Data Sheet	89-40001-00-405	SDS, xMAP® Sheath Fluid Concentrate PLUS, French (Switzerland)
Customer Instructions	**Sheath and Drive Fluid Flush Procedure**	
White Paper	**Introducing Sheath Fluid PLUS and Drive Fluid PLUS for xMAP® Systems**	

**All documents are available on the Luminex website.*

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