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UREA BIO EXCIPIENT

REAL TIME STABILITY REPORT: UR3200-025-0616

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of Urea Bio Excipient Grade material manufactured at BioSpectra's Stroudsburg, PA facility. Samples were placed on the Stability Testing Program in June of 2016 to fulfil the requirements of placing one lot of manufactured material per year on the Stability Testing Program. Testing intervals are designated by T_n , where n represents the number of months on stability. Testing was performed for a total of thirty-six months: every three months for the first year, every six months for the second year, and annually for each subsequent year, in order to assure that the manufactured product remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may be used to re-evaluate the retest period for future lots of manufactured material.

This Real-Time Stability Report assesses the stability of one lot of Urea, Bio Excipient that completed three years of long-term stability in June 2019. The stability study included the following analyses: Biuret, Conductivity, Moisture and Melting Range. In November of 2017, Assay and Impurities were added as a Stability Analysis for Urea. The result obtained for Organic Impurities accounts for any biuret within the product. Biuret was removed from the stability requirements between T_9 and T_{18} timepoints. Results from all analyses are summarized in Table 2, and Shelf-Life Plots have been predicted for all quantitative analyses. Shelf-Life Plots determine the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the Predicted Shelf-Life. This allows BioSpectra to ensure that the product will be stable over the time period in which it is part of the Stability Testing Program.

2. REFERENCES:

- 2.1. Current USP
- 2.2. ICH Q1
- 2.3. [Stability Testing Program](#)
- 2.4. [Stability Inventory](#)

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of one lot of Urea. Stability samples from this batch were put into four different packaging configurations. These samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configurations and descriptions. The type of packaging utilized in this stability study was based on BioSpectra final packaging offered to the customer.

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TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Fiber (P/F)	Samples are packaged into small poly bags and sealed with a zip tie. All individual samples are then placed into a fiber drum, along with a 4-unit desiccant.
Poly/Poly (P/P)	Samples are packaged into small poly bags and sealed with a zip tie. All individual samples are then placed into a poly drum.
Tyvek/Poly (T/P)	Samples are packaged into small tyvek bags and sealed with a zip tie. All individual samples are then placed into a poly drum, along with a 5x8-unit desiccant.
2 Tyvek/Poly (2T/P)	Samples are packaged into small tyvek bags and sealed with a zip tie. All individual samples are then placed into a larger tyvek bag with a 5x8-unit desiccant. This bag will then get placed into a poly drum.

4. STORAGE:

Samples were placed on stability in BioSpectra's Stroudsburg PA facility Stability Area, located in the quarantine area of the Warehouse. The USP Packaging and Storage requirements for Urea are 15-30°C. Storage conditions were continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor). The maximum temperature of the warehouse during the stability study was 28.14°C, and the minimum temperature of the warehouse was 12.63°C. See Section 5 for the Discrepancy Investigations initiated for temperature excursions.

5. INVESTIGATIONS:

- 5.1. SDI16-57 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the Urea stability samples, as the next time point, T₆, was pulled and tested without issue.
- 5.2. SDI18-01 was initiated for temperatures dropping below the minimum storage temperature of 15°C. The temperature excursion had no impact on the Urea stability samples, as the next time point, T₂₄ was pulled and tested without issue.

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6. LOT EVALUATION:**TABLE 2: ALL-INCLUSIVE STABILITY DATA**

Urea Bio Excipient Stability Data											
Lot Number	Analysis	Specification	T ₀ ¹	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	
UR3200-025-0616 P/F	Assay	98.0-102.0%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	100.07%	100.62%	99.37%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<i>No longer required</i>	<i>No longer required</i>	<i>No longer required</i>
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	12.12µS/cm @ 22.1°C	11.8µS/cm @ 22.3°C	20.3µS/cm @ 23.4°C	14.48µS/cm @ 23.8°C	16.0 µS/cm @ 21.3°C	14.0 µS/cm @ 20.5°C	16.3µS/cm @ 26.3°C	
	Moisture	0.5% max.	0.080%	0.040%	0.060%	0.060%	0.060%	0.060%	0.040%	0.060%	
	Melting Range	132-135°C	133.1-134.5°C	133.1-134.3°C	132.8-134.2°C	133.6-134.7°C	133.2-134.4°C	133.4-134.7°C	133.3-134.5°C	133.1-134.8°C	
	Impurities	Organic <0.1%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	0.05%	<0.1%	<0.1%
		Total <2.0%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<2.0%	<2.0%	<2.0%
Unspecified <0.1%		<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	0.000%	<0.1%	<0.1%	
UR3200-025-0616 P/P	Assay	98.0-102.0%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	100.21%	100.66%	99.77%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<i>No longer required</i>	<i>No longer required</i>	<i>No longer required</i>
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	12.08µS/cm @ 21.7°C	12.0µS/cm @ 22.4°C	18.8µS/cm @ 23.8°C	13.34µS/cm @ 23.7°C	16.3µS/cm @ 21.8	12.2µS/cm @ 20.7°C	14.5µS/cm @ 26.4°C	
	Moisture	0.5% max.	0.080%	0.060%	0.060%	0.060%	0.040%	0.060%	0.040%	0.060%	
	Melting Range	132-135°C	133.1-134.5°C	132.8-134.2°C	133.4-134.7°C	133.5-134.8°C	133.4-134.6°C	133.0-134.4°C	133.3-134.5°C	133.2-134.6°C	
	Impurities	Organic <0.1%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	0.06%	<0.1%	<0.1%
		Total <2.0%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<2.0%	<2.0%	<2.0%
Unspecified <0.1%		<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	0.000%	<0.1%	<0.1%	
UR3200-025-0616 T/P	Assay	98.0-102.0%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	99.82%	100.78%	98.71%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<i>No longer required</i>	<i>No longer required</i>	<i>No longer required</i>
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	12.64µS/cm @ 22.2°C	11.6µS/cm @ 22.0°C	15.2µS/cm @ 23.7°C	12.28µS/cm @ 23.8°C	14.3µS/cm @ 22.6°C	10.2µS/cm @ 20.3°C	15.0µS/cm @ 26.1°C	
	Moisture	0.5% max.	0.080%	0.040%	0.040%	0.060%	0.040%	0.060%	0.080%	0.040%	
	Melting Range	132-135°C	133.1-134.5°C	133.1-134.4°C	133.4-134.5°C	133.6-134.8°C	133.3-134.7°C	133.3-134.6°C	133.4-134.5°C	132.6-134.2°C	
	Impurities	Organic <0.1%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	0.05%	<0.1%	<0.1%
		Total <2.0%	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<2.0%	<2.0%	<2.0%
Unspecified <0.1%		<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	<i>Not yet required</i>	0.000%	<0.1%	<0.1%	

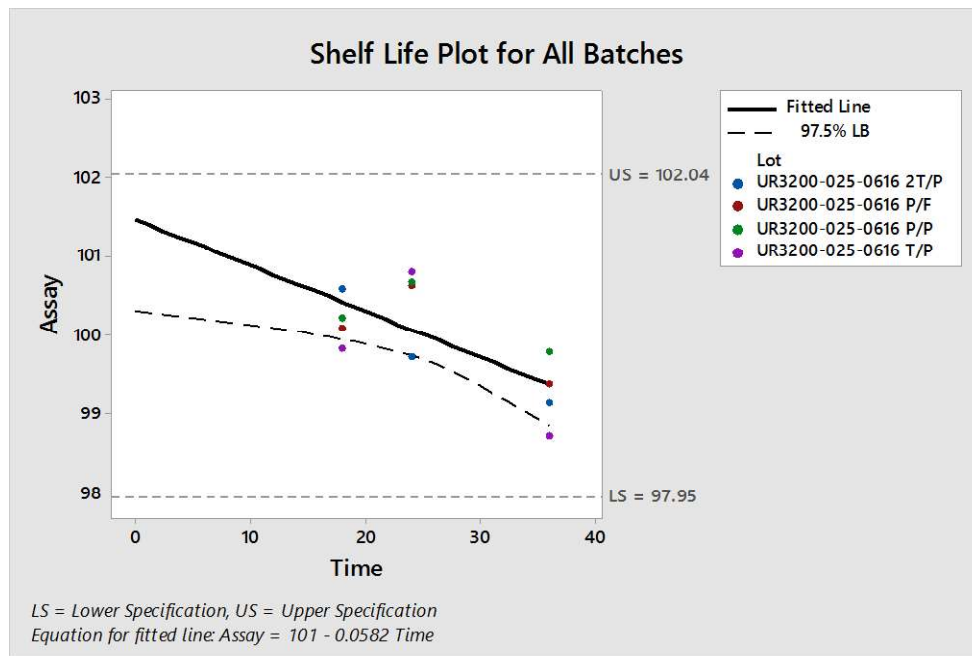
¹ Finished Goods testing was transcribed to summary sheets and will be used for T=0, as the testing is equivalent.

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Urea Bio Excipient Stability Data											
Lot Number	Analysis	Specification	T ₀ ¹	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	
UR3200-025-0616 2T/P	Assay	98.0-102.0%	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	100.58%	99.72%	99.14%
	Biuret	0.1% max.	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	No longer required	No longer required	No longer required
	Conductivity	30µS/cm max.	18.71µS/cm @ 19.8°C	11.33µS/cm @ 21.6°C	13.0µS/cm @ 21.8°C	17.0µS/cm @ 24.2°C	14.03µS/cm @ 23.7°C	13.8µS/cm @ 21.0°C	12.4µS/cm @ 20.3°C	14.5µS/cm @ 25.6°C	
	Moisture	0.5% max.	0.080%	0.060%	0.040%	0.060%	0.060%	0.060%	0.060%	0.060%	
	Melting Range	132-135°C	133.1-134.5°C	133.0-134.3°C	133.3-134.5°C	133.3-134.6°C	133.4-134.6°C	133.3-134.6°C	133.2-134.4°C	133.2-134.9°C	
	Impurities	Organic <0.1%	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	0.05%	<0.1%	<0.1%
		Total <2.0%	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	<2.0%	<2.0%	<2.0%
		Unspecified <0.1%	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	Not yet required	0.000%	<0.1%	<0.1%

¹Finished Goods testing was transcribed to summary sheets and will be used for T=0, as the testing is equivalent.

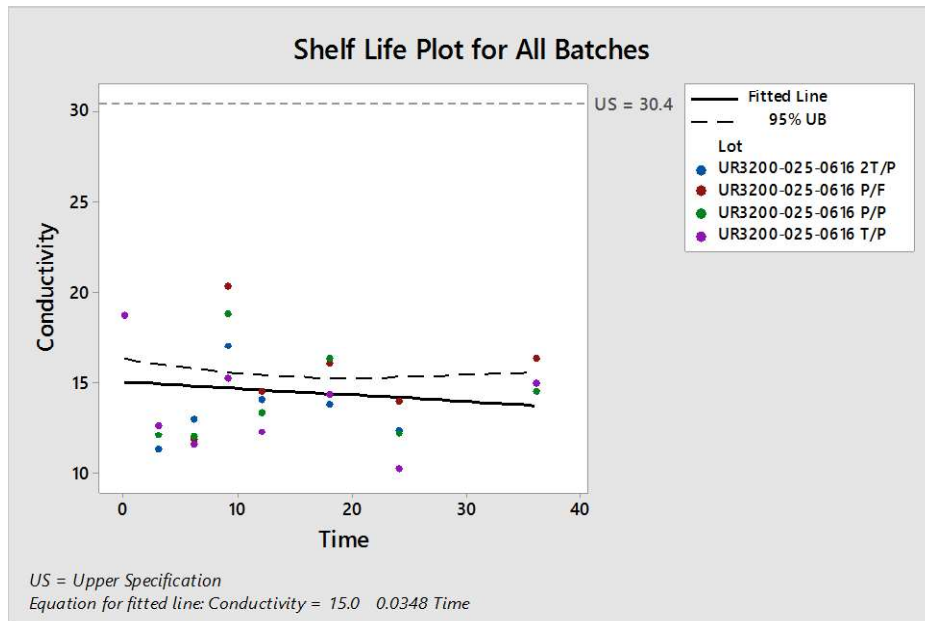
GRAPH 1: SHELF LIFE PLOT FOR ASSAY (%)



No Shelf-Life is able to be determined for Assay, as the mean slope response is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

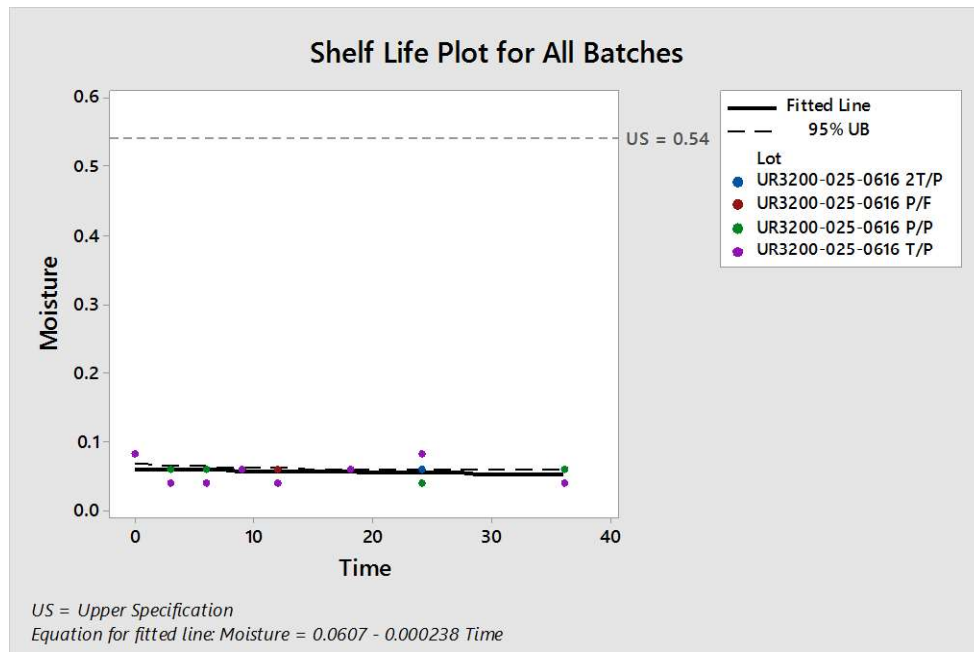
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GRAPH 2: SHELF LIFE PLOT FOR CONDUCTIVITY



No Shelf-Life is able to be determined for Conductivity, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

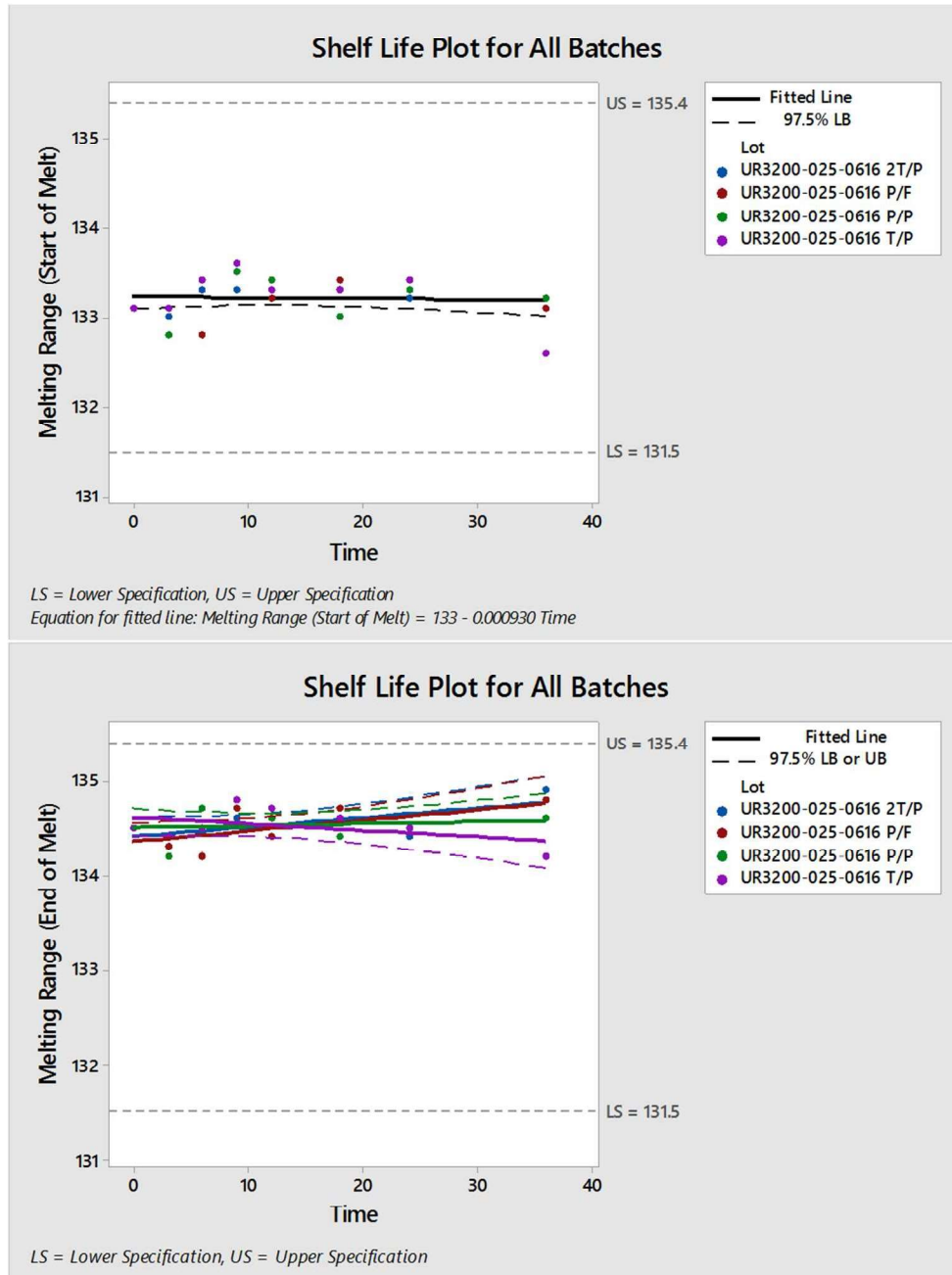
GRAPH 3: SHELF LIFE PLOT FOR MOISTURE (%)



No Shelf-Life is able to be determined for Moisture, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

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GRAPHS 4 AND 5: SHELF LIFE PLOT FOR MELTING RANGE



No Shelf-Life is able to be determined for Melting Range, as the mean slope is not significantly different from zero. There is no impact to the product or currently assigned expiration of this material.

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7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E 2.4.2.1, the retest date may be proposed for up to $2x$ where x is the period covered by long-term stability data, but should be no more than 12 months beyond. The data obtained during this stability study indicates that Urea Bio Excipient material is stable for 36 months in Tyvek/Poly, Poly/Poly, Poly/Fiber, and 2Tyvek/Poly packagings. The assigned re-test date of manufactured Urea Bio Excipient material will remain at 24 months unless otherwise requested on a lot-by-lot basis.

8. STATEMENT OF COMMITMENT:

8.1. BioSpectra is responsible for the following regarding Stability Data in this report:

8.1.1. In the event that any stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.

8.1.1.1. This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.

8.1.2. If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.

8.1.3. In the event that any out of specification results are confirmed, all authorized users of the material will be notified.

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