6.9 Current Regulatory Status
A thorough search for the current regulatory status of *M. alba* or its extracts, relevant to their use in food in the United States, was conducted. A summary of the pertinent search results is shown below:

- An FDA GRAS notice (GRN No. 000013) was found in the FDA GRAS Notices Inventory database for use of nine botanical ingredients, one of which was *M. alba*, as flavoring agents in herbal tea beverages. The basis of the GRAS conclusion was through experience based on common use in food. GRN No. 13 received FDA's 'no questions' response letter with respect to three of the notified botanicals on June 2, 1999; however, *M. alba* was among the six botanicals that were considered by the Agency to have insufficient history of use data to establish reasonable certainty of no harm for their intended use.

- Pursuant to 21 CFR part §184.1444 maltodextrin is GRAS for human consumption with no limitation other than current good manufacturing practice.

6.10 Basis for the GRAS Conclusion
Reducose® 5% has been the subject of a thorough safety assessment as described above. The totality of evidence supporting safety is comprised of data and information that establish the safety of Reducose® 5% under the conditions of its intended use and data and information that is corroborative of safety. The general availability and general acceptance, throughout the scientific community of qualified experts, of the data and information that establish the safety of Reducose® 5% under its intended conditions of use establish the general recognition of this data and information. Together, the establishment of safety based on scientific procedures and its general recognition form the basis for Phynova’s conclusion of GRAS status of Reducose® 5% for its intended use.

6.10.1 Data and Information that Establish Safety
The scientific data, information, and methods forming the basis of this conclusion are:

- The establishment of identity, demonstrating that Reducose® 5% is well characterized extract of *Morus alba* leaves containing 5 ± 0.5% DNJ, and spray dried on a maltodextrin carrier, which comprises approximately half of the final ingredient weight;

- The method of manufacture and specifications, demonstrating the safe production and robust quality control standards of Reducose® 5%;
• Known pharmacokinetic parameters of the DNJ marker, demonstrating reasonably similarities in laboratory animals and humans;
• The 28-day repeated-dose oral toxicity study in rats and dietary exposure estimate, establishing the lack of adverse health effects and or target organs of repeated exposure to Reducose® 5% in rats, and establishing an adequate margin of safety (MOS) for the intended conditions of use by humans of Reducose® 5% in food.

In the 28-day study, the NOAEL was 4000 mg/kg bw/day in male and female SPF Hsd.Han Wistar rats; the highest level tested. As the test item of the 28-day study contained L-leucine as a processing aid at an addition level of 6.5%, the equivalent NOAEL adjusted for the L-leucine content was 3740 mg/kg bw/day (4000 x 93.5%). Additionally, in terms of DNJ only, the NOAEL was 186 mg/kg bw/day (4000 x 4.65%) as the test item contained 4.65% DNJ. Based on the intended use of the ingredient in food in the categories and at the addition levels shown in Table 7 (also duplicated as Table 1), the NOAEL allows for an adequate MOS (NOAEL/Exposure; 4000 mg/kg/13.1 mg/kg) of approximately 305-fold in the general population when compared to the estimated human exposure level at the 90th percentile of consumers using a 10% presence probability factor, which supports a conclusion that the intended use of Reducose® 5% is reasonably certain to be safe. When adjusted for the added L-leucine, the MOS (3740 mg/kg/13.1 mg/kg) is approximately 258-fold and when expressed in terms of DNJ content (13.1 mg/kg x 4.5-5.5%) the MOS (186 mg/kg/0.590-0.722 mg/kg) ranges from approximately 258- to 315-fold. As Reducose® 5% is standardized to contain 5 ± 0.5% DNJ, the addition or removal of L-leucine does not impact the findings of the toxicology studies as the same amount of mulberry leaf extract (65.5%) and DNJ (4.65%) would have been present in the neat test item with or without the use of L-leucine, which would have been replaced with maltodextrin. Thus, regardless of L-leucine content, there is an adequate MOS and the conclusion that the intended use of Reducose® 5% is reasonably certain to be safe is supported.

6.10.2 Data and Information that is Corroborative of Safety
The safety of Reducose® 5% is corroborated by an acute oral toxicity study in mice in which the LD₅₀ was >5 g/kg bw. The safety of Reducose® 5% is also corroborated by toxicological tests on Reducose® 1% (a related ingredient produced by Phynova with a lower DNJ content) in which a bacterial reverse mutation test and in vivo mammalian micronucleus test collectively demonstrated a lack of genotoxic potential of the ingredient, a sperm deformity test in mice in which no adverse effects on sperm morphology were observed at doses up to 10 g/kg bw for five days, and no general toxicity was observed in 14-day and 30-day repeated-dose oral
toxicity studies in rats in which the MTD and NOAEL were determined as ≥15 g/kg bw/day and 7.5 g/kg bw/day, respectively. Additionally, the safety of Reducose® 5% is corroborated by toxicological studies on other M. alba leaf preparations (with and without known DNJ contents) and other substances rich in DNJ. Finally, the safety of Reducose® 5% is further corroborated by the lack of serious adverse events reported in clinical trials using Reducose® 5% or other M. alba leaf preparations at daily dosages up to 5 g and durations up to 6 months, and the history of human consumption of approximately 1015 kg of Reducose® 5% over a one-year period with no adverse event reported.

6.10.3 General Recognition
The scientific data, information, and methods herein reported, that provide the basis of this GRAS conclusion by scientific procedures are published and available in the public domain. Part 7 of this GRAS notice contains the citations for the published studies. These publicly available data and information fulfill the requirement of the GRAS standard for general availability of the scientific data, information, and methods relied on to establish the safety of Reducose® 5% for its intended conditions of use. The peer-review of the published studies and lack of Letters to the Editor or other dissenting opinions provide ample evidence of general recognition among qualified experts that there is reasonable certainty that consumption of Reducose® 5% for its intended use is not harmful. The general availability and acceptance of these scientific data, information, and methods satisfy the criterion of the GRAS standard that general recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use.

6.10.4 Data and Information that are Inconsistent with the GRAS Conclusion
In the diabetic rat drug interaction study by Huh et al. (2020), an MLE of unknown similarity to Reducose® 5% reduced clearance of Met in diabetic rats, possibly due to inhibition hOCT2 and/or hepatic cytochrome P450s. The study was discussed and placed in context in Subpart 6.4.2.

We have reviewed the available data and information and are not aware of any other data and information that are, or may appear to be, inconsistent with our conclusion of GRAS status.
6.10.5 Information that is Exempt from Disclosure under FOIA

There are no data or information in this GRAS notice that are considered exempt from disclosure under FOIA as trade secret or commercial or financial information that is privileged or confidential.
Part 7: Supporting Data and Information

Initial literature searches for the safety assessment described in Part 6 of this GRAS notice were conducted from October 2014 through November 2014. Additional literature searches were conducted from May 2015 through October 2015, January 2016 through October 2016, during March 2018, again from June 2019 through October 2019, and again on September 16, 2020.

7.1 Data and Information that are not Generally Available

Some of the data and information described in this GRAS Notice are unpublished and, therefore, are not generally available, as follows:

- The clinical trial PYN-IM-002a of Reducose 5% by Gallagher et al. (2015)
- The clinical trial PYN-IM-003 of Reducose 5% by Thondre et al. (2016)
- Sales and adverse event data reported by Phynova

The data and information cited above strengthen the weight of evidence and, thereby, corroborate the data and information that establish the safety of Reducose® 5% under the conditions of its intended use. We believe the safety conclusion can still be made even if qualified experts throughout the scientific community do not generally have access to this information.

7.2 References that are Generally Available

AIBMR Life Sciences, Inc.


