UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MOTIF FOODWORKS, INC.,

Petitioner,

v.

IMPOSSIBLE FOODS INC.,
Patent Owner.

U.S. Patent No. 11,013,250

"METHODS AND COMPOSITIONS FOR CONSUMABLES"

Inter Partes Review No. 2023-00208

DECLARATION OF DR. ROBERT MCGORRIN IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NOS. 9,943,096, 10,039,306, 11,013,250, 11,224,241

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I, Robert McGorrin, declare as follows:

1. I have been retained by Quinn Emanuel Urquhart & Sullivan LLP on behalf of Motif FoodWorks, Inc. ("Petitioner" or "Motif") as an independent expert in these *inter partes* review ("IPR") proceedings which are pending before the Patent Trial and Appeal Board ("the Board") of the United States Patent and Trademark Office (the "Proceeding").

2. I understand that, in these Proceedings, Motif is challenging the validity of claims 1-12 and 14-24 of U.S. Patent No. 9,943,096 (the "'096 patent") (EX1156), claims 1, 3–11, 13–14, 16–24, 26–27, and 29–33 of U.S. Patent No. 10,039,306 (the "'306 patent") (EX1157), claims 1, 3–13, and 15–23 of U.S. Patent No. 11,013,250 (the "'250 patent") (EX1001), and claims 1-23 of U.S. Patent No. 11,224,241 (the "'241 patent") (EX1159) (collectively, the "Challenged Patents" and "Challenged Claims"). Based on my review of the first page of these patents, I understand them to be assigned to Impossible Foods Inc. ("Patent Owner").

3. I am informed that the Challenged Patents have been asserted by Patent Owner against Motif in the co-pending litigation *Impossible Foods Inc. v. Motif FoodWorks, Inc.*, Case No. 22-cv-311 (D. Del.) ("Litigation"). I understand that the Litigation is proceeding in the District Court for the District of Delaware ("District Court"). I reserve the right to amend or supplement my opinions in this Declaration

in response to any positions that Patent Owner or its experts may take in the Litigation, or in response to any order of the District Court.

I. QUALIFICATIONS

4. Exhibit 1006 accompanying this Declaration is a true and correct copy of my current CV. It describes in greater detail my education, publications, employment and research history, and professional activities and awards.

5. I am presently a Professor of Flavor Chemistry in the Food Science & Technology Department at Oregon State University. I received a B.A. in Chemistry from Northwestern University in 1973, an M.S. in Organic/Medicinal Chemistry from the University of Illinois in 1976 and a Ph.D. in Organic/Medicinal Chemistry from the University of Illinois in 1980.

6. I am a nationally and internationally recognized expert and scholar in the field of flavor science, and have been actively involved in flavor research for more than 44 years. I have organized/co-organized eight flavor chemistry symposia and presented more than 15 invited symposium talks, and over 65 papers at national and international scientific conferences. My expertise is in the area of flavor chemistry, flavor technology, flavor analysis, and the chemistry and interactions among flavor and food components. This expertise is the result of my combined academic/food industry career as a professor at Oregon State University in Food Science with a specialty in Flavor Chemistry (2000-present), a senior research

scientist and section manager of the flavor group while at Kraft Foods, Inc. Research & Development (1981-2000), and a researcher on Maillard reactions and oat cereal flavor chemistry while employed as a research scientist in the flavor technology department at Quaker Oats Company Research & Development (1978-1981).

7. I have authored and co-authored numerous peer-reviewed scientific publications and technical book chapters relating to flavor chemistry, Maillard reactions, oat cereal chemistry, dairy flavors, and flavor-food interactions including but not limited to publications in well-respected scientific journals such as the *Journal of Agricultural and Food Chemistry*, *Analytical Chemistry*, *Journal of Food Science*, *LWT–Food Science and Technology*, and book chapters in the American Chemical Society Symposium Series. In addition, I have co-edited four books on flavor chemistry, two of which particularly involve Maillard reactions of heating foods such as meat to produce cooked beef flavors and aromas: T. H. Parliment, M. J. Morello, and R. J. McGorrin, Eds. *Thermally Generated Flavors: Maillard, Microwave, and Extrusion Processes*, ACS Books, Washington, D.C., American Chemical Society Symposium Series 543, 1994; T. H. Parliment, R. J. McGorrin, and C.-T. Ho, Eds. *Thermal Generation of Aromas*, ACS Books, Washington, D.C., ACS Symposium Series 409, 1989. I have published three chapters in flavor chemistry books about the subject of key impact flavor chemicals, also known as character-impact flavor compounds in foods, including Maillard-type, brown, and

meat flavors, a most recent example is: McGorrin, R. J., Character-impact flavor and off-flavor compounds in foods. In *Flavor, Fragrance, and Odor Analysis*, 2nd. ed, R. Marsili, Ed., CRC Press, Boca Raton, FL, 2012, Chapter 9, pp. 207-262. I also wrote a review chapter in a flavor chemistry reference book that described the occurrence of sulfur-containing flavor compounds in cooked beef and meat that are produced by Maillard reactions: McGorrin, R. J., The significance of volatile sulfur compounds in food flavors, In *Volatile Sulfur Compounds in Food*, M. C. Qian, X. Fan, and K. Mahattanatawee, Eds., ACS Symposium Series 1068, ACS Books, Washington, D.C., 2011, Chapter 1, pp. 3-31. These publications are included in my *curriculum vitae* which is attached as EX1006.

8. During my industrial career I received formal training and Flavor Profile certificates in the sensory descriptive analysis methods by Arthur D. Little (Boston, MA) and Sensory Spectrum (New Providence, NJ).

9. I have served on editorial boards for respected peer reviewed journals in the fields of food science, flavor science, and chemistry: *Journal of Agricultural and Food Chemistry* (24 years), *Chemosensory Perception* (15 years) and *Chemical Innovation* (5 years).

10. My professional achievements in flavor chemistry have been recognized by international scientific organizations. I am an elected Fellow of both the Institute of Food Technologists and the American Chemical Society. I received

the Distinguished Service Award in Agricultural and Food Chemistry from the American Chemical Society, and am a recipient of two Kraft Foods ABCD (Above and Beyond the Call of Duty) Awards. I am a Certified Food Scientist as conferred by the International Food Science Certification Commission.

11. In my extensive involvement in professional societies, I am a member of the Executive board and the Past-Chair and Program Chair of the American Chemical Society (ACS) Division of Agricultural & Food Chemistry (AGFD), served as the Chair of the ACS AGFD Flavor Chemistry Subdivision, am a professional member of the Institute of Food Technologists (IFT) and Past-Chairs of both the IFT Higher Education Review Board and the IFT Council of Food Science Administrators.

12. I frequently peer-review grant proposals submitted to the United States Department of Agriculture (USDA) and food commodity commissions, relating to research in the field of food and agriculture and topics including Maillard-generated flavors, and have served twice as a USDA panel manager for reviewing research proposals on Improving Food Quality.

II. SCOPE OF ASSIGNMENT

13. I have been asked to discuss principles of meat flavor chemistry and their application in food science, particularly relating to the chemistry of meat flavor and the preparation of meat replica products and meat flavor additives. In this

Report, I comment on certain relevant technical literature. I also draw upon my 44 years of experience in the field of food science and flavor chemistry.

14. I have been asked to review U.S. Provisional No. 61/751,816 (EX1025), which I refer to as the "816 Provisional," and to opine on whether its disclosure contains an adequate written description of the subject matter claimed in the Challenged Claims of the '096 and '241 patents.

15. I have been asked to review the prosecution history of the Challenged Patents, including certain experimental data and affidavits submitted by the Patent Owner in order to obtain the claims' allowance. I have been asked to provide my opinions on the experimental design disclosed in Patent Owner's submissions, the results obtained, the conclusions drawn from these results, and statements made by Patent Owner and its employees and experts during prosecution.

III. SUMMARY OF OPINIONS

16. In my opinion:

- The '816 Provisional's disclosure does not adequately describe the full scope of the Challenged Claims of the '096 and '241 patents. Although the claimed sugar and sulfur compounds were long used in the art to provide meaty and savory flavors to products, the '816 Provisional does not teach a POSITA (defined below) that these patents' named inventors possessed methods of using any combinations of these compounds, at any concentrations, under

particular conditions (such as cooking temperature, cooking time, moisture, and pH) to achieve a "beef-like" aroma in the context of the claimed foodstuffs.[1]

- A POSITA would reasonably expect success in producing volatile compounds associated with beef-like aroma in a foodstuff using sugars and sulfur-containing compounds, which are Maillard reaction precursors. E.g., the literature taught that "impact compounds" of meat such as 2-methyl-3-furanthiol (MFT) and bis(2-methyl-3-furyl)disulfide (MFT-MFT), as well as other volatiles associated with meaty aroma, are Maillard reaction products. Adjusting the pH, cooking time, cooking temperature, moisture, and other variables that could affect the production of volatiles would have been within the ordinary skill of a POSITA.

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[1] As discussed in Section IV.B below, I understand that to show adequate written description, the specification itself must demonstrate that the named inventors possessed the invention as of the time of the disclosure—information outside of the specification is not enough. I also understand that a description that merely renders the subject matter of patent claims obvious does not satisfy the requirement of showing possession of the invention for purposes of adequate written description support.

- A POSITA would not have been discouraged from adding a heme-containing protein ("heme-protein")—such as a native plant heme-protein like leghemoglobin or a recombinantly-produced native animal heme-protein like myoglobin—to a meat replica matrix, food flavor additive, or meat-like-food product due to concern that the heme-protein would lead to undesirable aroma. Although heme-proteins can promote lipid oxidation and undesirable flavors in meat and other products ***over time***, lipid oxidation contributes to a desirable meaty aroma upon initial cooking.
- To the extent the Challenged Claims were allowed because the Examiner believed the claims covered "novel" or unexpected results, in my opinion, this was an error. For multiple reasons explained below, the declarations and supporting evidence proffered by Patent Owner in support of the Challenged Claims' patentability are inadequate to demonstrate the production of a meaty, beef-like aroma in the context of the claims. Nor do these materials demonstrate production of "novel" volatile compounds in Patent Owner's claimed foodstuffs, as such compounds are produced via the Maillard reaction in the absence of heme-proteins. Patent Owner's contrary assertions during prosecution mischaracterize the significance of these proffered results.

IV. LEGAL UNDERSTANDING

17. In this section I describe my understanding of certain legal principles that I have relied upon in forming my opinions set forth in this Declaration. I have been informed of these legal standards by counsel for Motif. I am not an attorney and I have not researched the law on patent invalidity. I am relying only on Motif's attorneys regarding these legal standards.

18. I have applied the standards below in my analysis of the Challenged Patents.

A. Person of Ordinary Skill in the Art (POSITA)

19. I am informed that patent validity is determined from the perspective of a person of ordinary skill in the pertinent art at the time of the invention ("POSITA"). I understand that a POSITA is a hypothetical person who is presumed to be aware of all pertinent art, conventional wisdom in the art, and is a person of ordinary creativity—not an automaton.

20. In deciding the level of ordinary skill in the art, I am informed that the following factors may be considered:

- the levels of education and experience of persons working in the field;
- the types of problems encountered in the field;
- the sophistication of the technology.

B. Written Description

21. I am informed and understand that, under 35 U.S.C. § 112, a patent's specification is required to contain a written description of the invention. I am informed that the test for whether the written description is adequate is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.

22. I am informed and understand that this inquiry is a factual question and requires an objective inquiry into the four corners of the specification from the perspective of a POSITA. I further understand that demonstrating adequate written description of a genus requires a precise definition of the invention, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials. Relatedly, I understand that it is not sufficient for purposes of the written description requirement that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to the modifications that the inventor might have envisioned, but failed to disclose. I also understand that it is the specification itself, not information outside the specification, that must demonstrate possession, and that a description that merely renders the invention obvious does not satisfy the requirement.

C. Obviousness

23. I am informed and understand that, under 35 U.S.C. § 103, a patent claim is invalid if the subject matter of the claim as a whole would have been obvious to a person of ordinary skill in the art at the time of the invention. I further understand that the following factors must be evaluated to determine whether the claimed subject matter is obvious: (1) the scope and content of the prior art; (2) the difference or differences between each claim of the patent and the prior art; (3) the level of ordinary skill in the art at the time the patent was filed; and (4) any objective indicia of non-obviousness, also known as "secondary considerations." Such objective indicia include: long-felt but unresolved needs; commercial success; failure of others to solve the problem that the inventor solved; and surprising/unexpected results.

24. I am informed and understand that one way obviousness may be established is by finding that all claimed limitations are disclosed in the prior art, and that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so. I am further informed and understand that absolute predictability of success is not required, only a reasonable expectation.

25. I am informed and understand that, for objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a

nexus between the evidence and the merits of the claimed invention and that, where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.

V. MEAT FLAVOR CHEMISTRY

26. Below, I summarize certain principles relating to meat flavor chemistry.

A. Overview of Meat Aroma and Flavor

27. Flavor science involves the body's physiological response to aroma and taste. The flavor experience, which is mediated by olfactory and gustatory receptors, is generally understood to be comprised of approximately 80% volatile aroma compounds and 20% non-volatile tastants. For the aroma contribution, sensory scientists refer to aromas that we sense by smell as orthonasal (smelling by inhaling through the nose) and retronasal (aroma released inside the mouth during masticating and chewing of food that is sensed by olfactory receptors via the sinus passages.) Because aroma volatiles are predominant contributors to the flavor of food, flavor and aroma are highly linked. In flavor chemistry research, the terms "aroma" and "flavor" are often used interchangeably in recognition of the dominant contribution of aroma to total flavor.

28. To date, there are approximately 8,000 known volatile compounds that contribute aroma to food, and the five basic taste categories—sweet, sour, salt, bitter, umami—which provide taste sensations. Tastants alone have a supporting but limited contribution to complex flavors such as meat flavor. When consumers of foods state that "they don't *taste* good," what they are usually describing is the contribution of the aroma compounds is deficient, lacking, or unbalanced in the overall meat flavor.

29. Meat's aroma and flavor results from chemical reactions that, upon cooking, produce volatile compounds which are detected via smell and non-volatile compounds which are detected by taste. As explained by Dwivedi (EX1026, 487):

> The flavor of meat is attributed to a complex mixture of compounds produced by heating a heterogenous system containing nonodorous precursors, and it is comprised of: l. Volatile compounds with odor properties. 2. Nonvolatile compounds with taste and tactile properties. 3. Potentiators and synergists.

"Of these, the volatile compounds are by far the most important." EX1024(MacLeod), 310 (discussing "Natural Meat Flavor (With Particular Reference to Beef)"). These volatiles result from heating the meat, as "[m]eat flavour is thermally derived" and "uncooked meat has little or no aroma and only a blood-like taste." EX1017(Mottram), 415.

30. Aroma volatile constituents of food flavors such as beef flavor occur as complex mixtures at concentrations ranging from parts-per-million to parts-per-trillion. Many beef aroma volatiles contain sulfur compounds which have very low odor thresholds—i.e., they can be detected via smell when present at very low levels. These compounds are typically present in meat flavors at extremely low levels, often at sub parts-per-billion concentrations.

31. The relative sensory impact of an aroma compound depends on its individual odor threshold, and its concentration in the meat flavor. The concentration of an aroma compound is particularly important in the context of its sensory threshold. If the compound is present at concentrations below its odor threshold, it cannot be sensorially detected. If it is at its odor threshold, it will be weakly perceived (detection threshold), and if it is above its threshold it will be recognizable as a contributor to meaty flavor (recognition threshold).

32. The relative concentrations of aroma compounds need to be in balance, otherwise the flavor will be perceived as being harsh, "off", or incongruent with the overall characteristic it should convey.

1. Character-Impact Compounds and Meat Aroma Complexity

33. **Character-Impact Compounds**: Sulfur-containing heterocyclic compounds are associated with meaty characteristics. Some sulfur volatile compounds in meat flavor provide background sensory nuances to the flavor, while

other sulfur volatiles provide unique flavor characterizing identities to the meat flavors they occur in. The latter unique flavor substances are referred to as "character-impact compounds." EX1031(McGorrin), 4; EX1039(McGorrin), 207.

34. When smelled or tasted, a single character-impact aroma chemical or blend of characterizing chemicals contributes a recognizable sensory impression at the typically low concentration levels in natural flavors. Examples of sulfur-containing character-impact compounds in meat flavor include 2-methyl-3-furanthiol [MFT] ("roasted meat" character) and bis-(2-methyl-3-furyl)disulfide [MFT-MFT] ("aged beef" character).

35. MFT has an aroma detection threshold of 1 part-per-trillion, and the corresponding disulfide dimer (MFT-MFT), with an aroma detection threshold of 0.02 parts-per-trillion. EX1017(Mottram), 418; EX1034(Reineccius), 264; EX1031(McGorrin), 18 (citing EX1119(Boelens), 32). Both MFT and MFT-MFT have been identified in cooked beef and chicken broth and have a strong meaty quality upon dilution. MFT also occurs in canned tuna fish aroma. *See* EX1095(Withycombe). The MFT-MFT disulfide has a recognizable aroma character of "rich aged-beef, prime-rib." EX1031(McGorrin), 18. These compounds can be formed in heated model systems via Maillard reactions containing hydrogen sulfide or cysteine and pentoses or other sources of carbonyl

compounds. EX1017(Mottram), 418-19. They can also be produced from thermal degradation of thiamine (vitamin B1). EX1017(Mottram), 419.

36. Other potent sulfur-containing odorants 2-furfurylthiol, 2-mercapto-3-pentanone, and 3-mercapto-2-pentanone have been identified in heated meat. EX1096(Kerscher). A related sulfur volatile, 2-methyl-3-(methylthio)furan is the character-impact compound for roast beef. EX1031(McGorrin), 18; EX1031(McGorrin), 18 (citing EX1119(Boelens), 32).

37. Additionally, in cooked meats and other thermally processed foods, the key aroma compound 2-acetyl-2-thiazoline imparts a potent "roasty, popcorn" note that enhances meaty and roast flavors. It was first identified in meat systems among the flavor volatiles of beef broth, and later reported as one of the character-impact compounds of roasted beef. EX1039(McGorrin), 231; EX1039, *citing* EX1039(Cerny), 2714. 2-Acetyl-2-thiazoline was subsequently detected as a potent odorant of chicken broth and cooked chicken. EX1039(McGorrin), 231; EX1096(Kerscher), 1955. A related compound, 2-acetylthiazole, has a "nutty" and "popcorn aroma" and a higher odor threshold than 2-acetyl-2-thiazoline. EX1039(McGorrin), 233.

38. As a class, volatile sulfur compounds exhibit sensory potency at low levels because of their low aroma and taste thresholds. As Manley recognizes:

> Typically, less than 0.1 percent of a powerful aroma is necessary to be present in a food to act as a flavor. This is particularly true in the savory/meat flavor area where some of the flavoring components have odor thresholds in the part per billion and trillion level!

EX1038(Manley), 139.

39. In most situations—for meat as well as other kinds of foodstuffs—these compounds change the sensory impression depending on the concentration in which they are present in the flavor mixture.

> Character compounds which contribute positive flavor impact at low levels can become off-flavors when they occur at higher concentrations. For example, dimethyl sulfide provides an appropriate "corn-like" background character to beer flavor at low levels, however it contributes a highly undesirable "cooked vegetable" or "cabbage-like" malodor when present at levels significantly above its sensory threshold …. Similarly, for cheddar cheese flavor, it imparts a rotten vegetable taste when present at high levels.

EX1031(McGorrin), 24.

40. In particular, if sulfur volatiles occur in meat aromas at concentrations which are too high, then they can change the aromas' characteristics to unpleasant and inappropriate sulfury-mercaptan notes which contribute to off-flavors and taints. EX1031(McGorrin), 16. For example, at typically low levels, MFT may exhibit a "roasted meat" flavor characteristic, but at high concentrations it would be perceived as "sulfurous and objectionable." EX1017(Mottram), 418; EX1119(Boelens), 32.

41. **Other Aroma-Associated Volatiles**: The aroma of meat is complex, however, and many more volatile compounds are associated with meaty aroma than character-impact compounds. For decades, researchers have recognized that hundreds of individual volatile chemical compounds are associated with meaty aroma. For example, MacLeod recites an "extremely long" list of more than 450 "aroma compounds so far identified from cooked beef," (EX1024(MacLeod), 312, Table1), and a similar list is found in Table 1 of Dwivedi (EX1026) (reciting "Volatile Compounds Isolated from Heat-treated Beef"). According to Mottram, "[a]n examination of the literature relating to the volatile compounds found in meat, shows that over 1000 volatile compounds have been identified." EX1017(Mottram), 415.

42. In my experience, these compounds are associated with and contribute to the background perception of the overall meaty or beef-like aroma, even if they are not considered character-impact compounds.

43. **Relevance to Challenged Claims:** I have reviewed the Challenged Claims. Based on my review, it is my understanding that they do not recite or require production of character-impact compounds associated with meaty or beef-like aroma. However, as a POSITA would recognize, the production of character-impact compounds, and their relative amounts and proportion in the overall profile of

volatiles, would be relevant to the production of improved or "more accurate" meaty or beef-like aroma.

B. Maillard Reaction and Meat Flavor

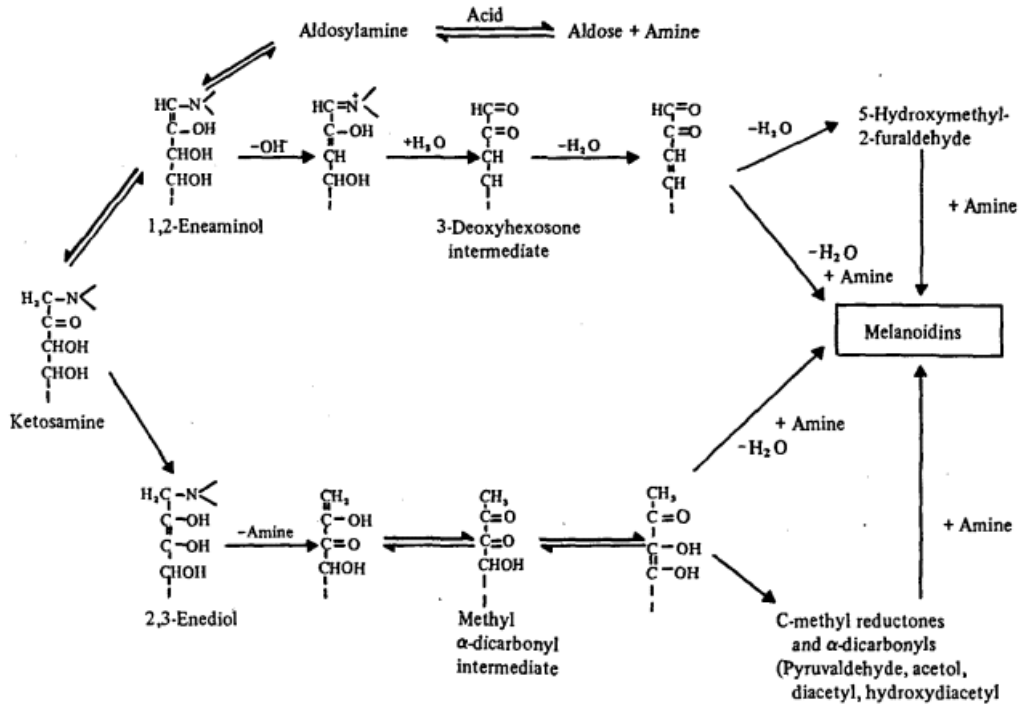
44. The Maillard reaction (non-enzymatic browning) is a series of reactions that begins with a carbonyl group (e.g., sugar) and an amino group (e.g., amino acid). The reaction is beneficial during cooking to develop roasted, baked, toasted, etc. flavors and aromas accompanied by brown colors on inner and outer surfaces of foods. As explained in Calkins (2007) (EX1028, 65):

> The Maillard reaction, or nonenzymatic browning, helps explain amine and carbonyl reactions in food. In general, amino compounds condense with the carbonyl group of a reducing sugar in the presence of heat. This produces gylcosylamine [sic] which is rearranged and dehydrated to form furfural, furanone derivatives, hydroxyketones, and dicarbonyl compounds. All of these compounds contribute to flavor.

45. As I discuss further below, volatile meat flavor compounds formed during cooking are the products of Maillard reactions between sugars and amino acid precursors in lean (muscle) tissues that are derived from breakdown of meat proteins to generate "meaty" flavors. The Maillard reaction is not the only reaction that contributes to meaty aroma, however. Fatty (adipose) tissues also provide the flavor characteristics for a particular meat species (e.g., beef, lamb, pork, etc.) from thermal oxidation of lipid and phospholipid constituents. EX1017(Mottram), 421-22.

46. **Maillard Reaction:** The Maillard reaction, which occurs between amino compounds and reducing sugars, has been recognized for over 60 years as one of the most important routes to flavor and browning in cooked foods. EX1099(Mottram), 269. Thermal reactions between amino acids and carbonyl compounds were first observed by Strecker in 1862, who described the formation of aldehydes through oxidative degradation of amino acids. In 1912, Maillard reported the formation of color through the interaction of amino acids with glucose. EX1099(Mottram), 270.

47. In 1953, a scheme was reported to explain the essential steps in this reaction. EX1099(Mottram), 270. This scheme still forms the basis of what scientists today understand as the Maillard reaction. A depiction of its steps is reproduced below.



EX1026(Dwivedi), 529 (Figure 10, Mechanism of the Maillard reactions).

48. **Precursors:** To create the volatile chemical compounds that produce meat flavor and aroma, other chemical compounds termed "flavor precursors" must be chemically reacted using heat.

49. These precursors are found naturally in meat. EX1026(Dwivedi), 487 ("Because it is necessary to heat meat to produce the desired flavor, it follows that meat must contain substances which interact or degrade during cooking to produce compounds responsible for the characteristic flavor of meat. These substances are termed flavor precursors.").

50. Key precursors include amino acids, such as cysteine and methionine, and various sugars. Dwivedi explains, for example, that "[t]he carbohydrates present

in raw meat interact with amino compounds and produce volatile flavor compounds via Maillard reactions." EX1026(Dwivedi), 502 ("[F]lavor precursors are produced in an animal body. It is quite clear … that meat flavor precursors include amino acids, small peptides, carbohydrates, particularly hexoses and pentoses, and nucleotides …."); EX1024(MacLeod), 362-63 & Table 3.

51. Meat contains various kinds of carbohydrates (sugars): "[s]ugars and sugar phosphates identified from meat extracts include: fructose, fructose-6'-phosphate, fructose-1,6'-diphosphate, glucose, glucose-6'-phosphate, ribose, and ribose-5' phosphate." EX1026(Dwivedi), 503; EX1024(MacLeod), 366 ("[N]ucleotides are potential sources of reducing sugars, in particular free ribose and ribose phosphate—well-known Maillard reaction participants." (footnote omitted)). As shown below in Dwivedi Table 3 (EX1026), meat also contains sulfur-containing amino acids such as cysteine and methionine.

TABLE 3

Potential Flavor Precursors Isolated from Meat Extracts

Alanine	Fructose-6'-phosphate	Lysine
β-Alanine	Glucose	Methionine
quaternary Amines	Glucose-6'-phosphate	Methylhistidine
Ammonia	Glutamic acid	Nicotinamide-adeninedinucleotide
Anserine	Glutamine	Ornithine
Arginine	Glutathione	Peptides
Asparagine	Glycerophosphoethanolamine	Phenylalanine
Aspartic acid	Glycine	Phosphoethanolamine
Carnitine	Glycoproteins	Phosphoserine
Carnosine	Histidine	Proline
Citrulline	Hydroxyproline	Purine-nucleosides
Creatine	Hypoxanthine	Purine-nucleotides
Creatinine	Inosine-5'-monophosphate	Ribose
Cysteine	and other nucleotides	Ribose-5'-phosphate
Cystine	Isoleucine	Serine
Fructose	Leucine	Taurine
		Threonine
		Tyrosine
		Urea
		Valine

52. Thiamine, also known as Vitamin B_1, can also be used in the Maillard reaction. EX1026(Dwivedi), 501 ("The use of thiamine as one of the ingredients used in the preparation of synthetic meat flavors is not surprising. Thiamine, like cystine and cysteine, on heating produces a number of sulfur compounds that contribute significantly in meat-like synthetic flavor formulations.").

53. It has been proposed that ribose phosphate is the principal precursor of furan and thiophene (thiophen) thiols—e.g., MFT and MFT-MFT. EX1017(Mottram), 419 ("Dephosphorylation and dehydration of ribose phosphate form the important intermediate 4-hydroxy-5-methyl-3(2H)-furanone, which readily reacts with hydrogen sulfide.").

54. **Reaction Products:** Many of the volatile compounds associated with meaty and beef-like aroma have long been recognized to be products of the Maillard reaction. As excerpted below, Mottram and others recognized the importance of this reaction in generating meaty flavor.

> ***The Maillard reaction, which occurs between amino compounds and reducing sugars, is one of the most important routes to flavour compounds in cooked foods, including meat.*** This reaction is complex and provides a large number of compounds which contribute to flavour.

EX1017(Mottram), 417 (citations omitted).[2]

[2] Unless otherwise indicated, all emphasis is added.

> Fresh raw meat has little or no odor and so the aroma components of Table 1 ["Volatile Compounds of Natural Beef Aroma"] develop during heating, either directly or indirectly from the nonvolatile precursors already described…. Primary reactions occurring on heating include degradation of sugars, pyrolysis of proteins and amino acids, and lipid degradation. Additionally, interreaction [sic] of two or more precursors may occur, as in the Strecker degradation, Maillard reaction, and protein/ lipid interactions.

EX1024(MacLeod), 367.

55. The practical significance of the relationship between the Maillard reaction and meaty aroma is manifested in the number of patents owned by commercial entities covering aspects of this relationship.

> The importance of the flavor precursors … in the formation of meat flavor may be easily recognized by the fact that a large number of patents on meat flavoring compositions, which are based on the heat treatment of flavor precursors, have been awarded in the last few years. Some of the patents are based on the Maillard reactions between sugars and amino compounds.

EX1026(Dwivedi), 500.

> Studies of the aromas produced on heating mixtures of amino acids and sugars, confirmed the important role played by cysteine and ribose in meat flavour formation and led to the classic patent of Morton *et al.* (1960) which involved the formation of a meat-like flavour by heating a mixture of these compounds. Most subsequent patent proposals for

> 'reaction product' meat flavourings have involved sulfur, usually as cysteine or other sulfur-containing amino acids.

EX1017(Mottram), 416 (citations omitted).

1. Factors Affecting Maillard Chemistry

56. The components of the raw meat, and the manner of their chemical reorganization during cooking (degradation, recombination with other components) contribute to the complexity of meat flavor and aroma. The reaction rate of the Maillard reaction is influenced by factors such as the amount(s) and identity of the precursor compounds, cooking temperature, pH, cooking time, and water activity (amount of available moisture).

57. **Cooking Time and Temperature:** As noted by Gary Reineccius, "[t]he time and temperature of heating strongly influence the flavor character of the process flavoring." EX1034(Reineccius), 271.

58. Temperature is a principal driver of the Maillard reaction. As examples, in my experience, typical temperatures for roasted flavors and aroma occur well above 100 °C; stewed meat flavors are the result when the water activity is 1.0 and the temperature does not exceed 100 °C. Lower water activity and higher food surface temperatures favor the production of roasted flavor compounds from the same reactants, rather than the production of stewed meat flavors. EX1034(Reineccius), 271.

59. A POSITA would have understood that different pathways of flavor formation have different activation energies. For example, pathways that result in the formation of pyrazines (a class of thermally-generated aroma volatiles) have a high activation energy, which means that the amount of these volatiles produced rapidly increases with increasing temperatures. EX1033(Reineccius), 106-07 (Figure 5.3 showing the influence of temperature on the rate of formation of pyrazines, which is significantly more at temperatures greater than 150º C). It was well known that pyrazines are associated with the aroma of cooked meat, and, in particular, contribute roasted, nutty, and toasted notes. *See, e.g.*, EX1024(MacLeod), 344, Table 1 (pyrazine is a volatile component of "natural beef aroma"), 358 ("[B]asic fraction may contribute to roasted beef aroma and normally contains pyrazines …."), 384-385 (Tables 14 and 15 identifying various pyrazines that are produced when reacting cysteine, glucose, and ribose); EX1026(Dwivedi), 493 (identifying pyrazine and various derivatives as volatiles associated with heat-treated beef); EX1033(Reineccius), 107 ("These high activation energies indicate a very strong temperature dependence of pyrazine formation and explain why most pyrazines (roasted, nutty, toasted notes) are not formed during storage but only during high temperature treatment.").

60. **pH:** The effect of pH is also significant; optimum pH ranges between 5-7 favor the reaction, however basic pH (8 – 10) ranges can significantly increase

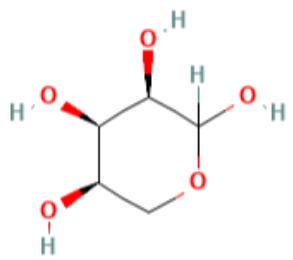
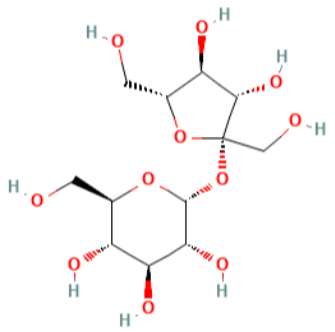
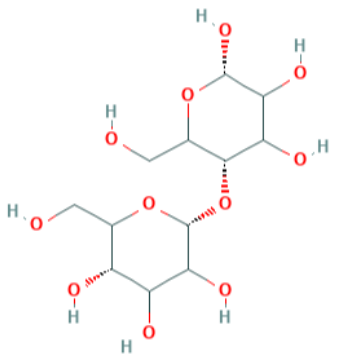
the formation of heterocyclic flavor compounds such as pyrazines. With changes in pH, some Maillard reaction pathways are enhanced, while others are retarded or unaffected. Because pH may strongly influence the ***balance*** of aroma compounds in a heated food, small changes in pH may significantly influence the aroma profile after heating. EX1034(Reineccius), 271.

61. **Moisture:** Moisture content can also affect the production of Maillard volatiles. Dwivedi observed, for example, that "[t]he differences in flavor due to cooking are probably a direct function of temperature and degree of moisture in the meat." EX1026(Dwivedi), 487.

62. **Precursor Structure:** The structure of sugars is known to affect their reactivity with amino acids in the Maillard reaction to generate cooked, roasted, etc. flavors and aromas. Pentose sugars (e.g., ribose, xylose, or arabinose) react more readily in comparison with hexose sugars (e.g., fructose, glucose). Monosaccharides react more readily in the Maillard reaction than disaccharide sugars (e.g., maltose, sucrose). EX1151(Ames), 151.[3]

[3] I was personally aware of the Ames publication prior to 2013 and would have been able to locate it prior to 2013 with the exercise of reasonable diligence.

63. Although these groups of molecules share some similarities, they are different chemical molecules. Below I show differences in the structures of certain sugar molecules:

Ribose	Sucrose	Maltodextrin
		

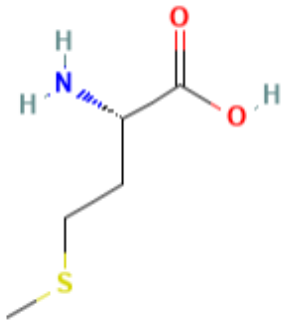
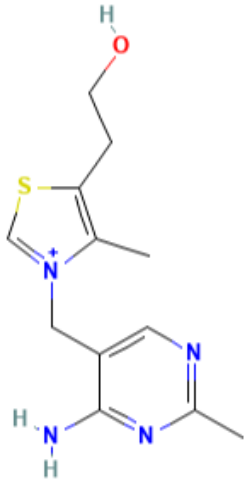
64. As shown above, for example, the sugar ribose is a 5-carbon sugar (pentose), whereas the sugar sucrose is considered a "glycosyl glycoside" or "disaccharide" formed by joining smaller 6-carbon (hexose) sugar molecules (glucose and fructose). The sugar "maltodextrin" also has a relatively complex sugar structure, as it is comprised of chains of glucose units.[4]

65. Similarly, some of the sulfur-containing precursor molecules that can be used in the Maillard reaction are shown below[5]: for example, cysteine, methionine, and thiamine. Methionine and cysteine are amino acids that contain a

[4] EX1111; EX1112; EX1109.

[5] EX1108; EX1110; EX1152.

sulfur atom. Thiamine, also known as Vitamin B_1, is chemical compound that contains a sulfur atom.

Cysteine	Methionine	Thiamine
		

66. These sugars and sulfur compounds can be added to a food product, such as meat, to serve as precursors for the Maillard reaction.

67. The selection of particular sugars and sulfur compounds is significant because—as with any chemical reaction—the end products of the Maillard reaction in a food product depend on the identity of precursor molecules that are reacted. Calkins (2007) explains:

> Different sugars and amino groups can produce different end products. Cysteine and glucose produce mainly sulfur compounds whereas cysteine and glucose under oxidized conditions produce more pyrazines and furans. Maillard volatile compounds from glutathione and glucose produce sulfur-containing compounds – thiophenes, thiazoles, and cyclic polysulfides – at pH 6 and 8, but furans are more often the end

> products at more acidic pH.… Cysteine and ribose, through the Maillard reaction, as well as thiamin have been shown to create compounds such as 2-methyl-3-furanthiol.

EX1028(Calkins), 65 (citations omitted).

68. As examples, MacLeod (1981) discloses a variety of volatile Maillard reaction products that are generated following the specific combination(s) of either cystine or cysteine with the sugar glucose (Table 14) or with the sugar ribose (Table 15), excerpted below. Table 14 of MacLeod provides (EX1024, 384):

Table 14
SOME VOLATILE REACTION PRODUCTS OF GLUCOSE/CYSTEINE AND OF GLUCOSE/CYSTINE

Glucose/cysteine	Glucose/cystine
Ethanol[197]	Ethanol[197]
But-2-en-1-ol(crotyl alcohol)[198]	Propanone[199]
Acetic acid[197]	Acetic acid[197]
But-2-en-1-al(crotonaldehyde)[198]	Furfural[197]
Propanal[199]	Furfuryl alcohol[197]
Hexanal[198]	Furfural alcohol[197]
Butanone[198]	5-Methylfurfural[197]
Methylvinylketone[198]	5-Ethyl-2-methylfuran[197]
Buta-2,3-dione (diacetyl)[198]	Pyridine[197]
Penta-2,3-dione[198]	3-Methylpyridine (β-picoline)[197]
Cyclopentanone[198]	5-Ethyl-2-methylpyridine[197]
Cyclohexanone[198]	Methylpyrazine[197]
Benzene[198]	Methanethiol[199]
Toluene[198]	Ethanethiol[199]
m-Xylene[198]	Propanethiol[199]
p-Xylene[198]	2-Methylthiazole[197]
Benzaldehyde[198]	2,4(or 5) Dimethylthiazole[197]
Furfural[198]	2-Methyl-4-(or 5)ethylthiazole[197]
5-Methyl-2-furfural[198]	Trimethylthiazole[197]
2-Acetylfuran[197,198]	2-Methylthiazoline[197]
2-Acetyl-5-methylfuran[197,198]	
Pyridine[197]	
2-Methylpyridine (α-picoline)[197]	
3-Methylpyridine (β-picoline)[198]	
Methylpyrazine[197]	
2,5-Dimethylpyrazine[197]	
6-Ethyl-2-methylpyrazine[197]	
3-Ethyl-2-methylpyrazine[197]	
2,5-Dimethyl-3-ethylpyrazine[197]	
Methanethiol[199]	
Propanethiol[199]	
Pentanethiol[199]	
Thiophen[197,198]	
Hydroxythiophen[197]	
2-Methylthiophen[198]	
3-Methylthiophen[198]	
2-Ethylthiophen[198]	
2,3-Dimethylthiophen[198]	
2,5-Dimethylthiophen[198]	
2-Thiophenthiol[198]	
3-(Methylthio) thiophen[198]	
2-Formylthiophen[198]	
2-Formyl-5-methylthiophen[198]	
2-Acetylthiophen[198]	
2-Propionylthiophen[198]	
Dihydro-3(2H)thiophenone[198]	
2,3-Benzothiophen[198]	
Thieno [3,2,*b*] thiophen[198]	
2-Methylthiazoline[197]	

69. In contrast, Table 15 of MacLeod provides (EX1024, 385):

Table 15
SOME VOLATILE REACTION PRODUCTS OF CYSTEINE/CYSTINE-RIBOSE[200]

Carbon disulfide	2,6-Diethyl-3-methylpyrazine
Hydrogen sulfide	2-Acetylpyrazine
Methanethiol	2-Acetyl-3-methylpyrazine
Ethanethiol	6,7-Dihydro-5H-cyclopentapyrazine
Propan-1-thiol	2-Methyl-6,7-dihydro-5H-cyclopentapyrazine
Acetaldehyde	2-Formylthiophen
Methylamine	3-Acetylthiophen
Propylamine	2-Formyl-5-methylthiophen
Pentylamine/isopentylamine	2-Formyl-3-methylthiophen
Furfural	3-Acetyl-2-methylthiophen
Furfuryl alcohol	2-Acetyl-5-methylthiophen
2-Acetylfuran	5-Acetyl-2-methylthiophen
1(2-Furyl)-2-propanone	Thieno[3,2-*b*]thiophen
trans-1,2-(2,2′-Difuryl)ethene	Thieno[3,4-*b*]thiophen
Pyrrole	3-Methyl-1,2,4-trithiane
2-Formyl-1-methylpyrrole	2-Methylthiazole
2-Acetylpyrrole	5-Ethylthiazole
1-Furfurylpyrrole	5-Ethyl-2-methylthiazole
2-Methylpyridine	2,4,5-Trimethylthiazole
5-Ethyl-2-methylpyridine	2,4-Dimethyl-5-ethylthiazole
Methylpyrazine	2-Acetylthiazole
Propylpyrazine	2-Propionylthiazole
Alkylpyrazine	2-Butyrylthiazole
2,5-Dimethylpyrazine	2-(2-Furyl)thiazole
2-Ethyl-6-methylpyrazine	

70. As potential explanations for the variable nature of meat flavor, Dwivedi observed "that there must be a significant difference either in the proportion in which these compounds are present or in the way in which they interact." EX1026(Dwivedi), 487.

C. Heme Iron Catalysis and Lipid Oxidation

71. When meat is initially cooked, lipids (e.g., fatty acids) present in the meat oxidize, leading to desirable meat-associated aromas. Mottram explains, for example, that phospholipids "may also provide ***lipid oxidation products during the initial cooking of meat which contribute to desirable aromas***." EX1017(Mottram), 420. Over time, however, oxidation of unsaturated (double-bond containing) fatty acids in meat can lead to undesirable "warmed-over" flavors ("WOF").

> Phospholipids are essential structural components of all cells and contain a much higher proportion of unsaturated fatty acids than the triglycerides, including significant amounts of polyunsaturated fatty acids such as arachidonic acid (20:4). This makes them more susceptible to oxidation during heating and they have been associated with the off-flavour, known as 'warmed-over flavour', which develops in re-heated cooked meats.

EX1017(Mottram), 420. Thus, warmed-over flavor/WOF is a common descriptor for the off-flavor produced in meat a day or two ***after*** it has been cooked.

> The term [WOF] was coined … to describe the rapid development of oxidized flavor in cooked meat ***upon subsequent holding***. The rancid or stale flavor becomes readily apparent ***within 48 h***.

EX1048(Pearson), 287.

72. Heme-containing proteins, which are naturally present in meat (e.g., hemoglobin and myoglobin) have been implicated in WOF development. However, literature studies on cooked meat have demonstrated that myoglobin *per se* is not the catalyst of lipid oxidation in thermally-treated meat. Rather, cooking denatures (destroys the structure of) myoglobin, causing it to release its iron (Fe^{+2}) which then catalyzes the development of WOF in the meat.

> Results demonstrate that Mb [myoglobin] per se is not the catalyst of lipid oxidation in cooked meat. However, ***cooking destroys part of the Mb, releasing Fe^{2+}*** which then catalyzes the development of WOF.

EX1048(Pearson), 292. Before 2013, the art recognized various methods to slow down the development of WOF. One method of slowing WOF development is to include an antioxidant in the product. *Id.*, 298 ("A great deal has been written about the primary antioxidants, which may be used to inhibit development of WOF."). Notably, Maillard reaction products—contributed by heat-reacting the claimed sugars and sulfur compounds—can slow down lipid oxidation due to their antioxidant properties when cooked at high heat.

> Certain products of the Maillard reaction are known to have antioxidant properties and are produced during retorting of meat…. [A] temperature of about 90 °C is required to produce the browning compounds responsible for the antioxidant activity in cooked meat…. [T]here is a relationship between antioxidant activity and development of the brown color …. [T]he strong inhibitory action of the Maillard reaction products against WOF suggests that they could be useful in preventing development of WOF ….

EX1048(Pearson), 297-98.

D. Simulated Meat Flavoring Compositions

1. History

73. The first attempts to mimic meat flavors were made thousands of years ago. EX1024(MacLeod), 397. At the time, meat flavorings were in the form of blended spices, the selection and proportion of which was determined by the types of meat they were trying to mimic. *Id.*

74. Starting about 1865, food processors began manufacturing "meat extracts." *Id.* At first, these meat extracts were derived from real meat. *Id.* However, the process of manufacturing meat extracts was expensive and time-consuming. *Id.* Hence, food processors started exploring alternative ways to manufacture meat flavors. *Id.*

2. Reaction Product-Based Meat Flavoring Compositions

75. The era of meat flavorings-related research based on reasonably sound chemical analysis began in the 1950s. EX1024(MacLeod), 399. One breakthrough came when "the importance of reducing sugars and amino acids and the significance of Maillard reaction" was recognized to produce meat-like aromas and flavors. *Id.* This research led to many patents for simulated meat flavorings starting in the 1960s. *Id.*

76. The first "reaction products" patent was issued to Morton et al in 1960. Inventors "stressed the relevance of amino acids (in particular cysteine) and ribose (*per se* or from autolyzed nucleotides)" and prepared the very "first of the new type of imitation beef flavors … by heating aqueous mixtures of ribose, cysteine, β-alanine, glutamic acid, and tryptophan." *Id.* Researchers also observed that "[w]henever cysteine was used, recognizable beef aroma resulted and a large number of sulfur volatiles and carbonyl compounds, including furfurals were identified." *Id.* Indeed, cysteine in combination with various sugars and other compounds has been

proven to generate distinct meat-like flavors, including chicken, beef, roasted beef, cooked beef, and other flavors. *See id.*, 400-07 & Table 17.

> Even a cursory glance at Table 17 indicates how frequently cysteine has been selected as a component of thermally produced meat flavorings. It is the paramount source of sulfur-containing volatiles and is active either in the free form or within the tripeptide glutathione or as part of proteinaceous materials such as HVP. Of all the amino acids naturally occurring in meat, cysteine and cystine yield the meatiest odors when subjected to thermal processing, although cystine is not as satisfactory as cysteine, since it does not so readily undergo Strecker degradation. This unique role of cysteine is noteworthy and possible explanations of its importance have been offered. The most crucial feature is the formation of many highly reactive and odorous compounds resulting from its pyrolysis, Strecker degradation and Maillard reaction.

EX1024(MacLeod), 408 (footnotes omitted).

77. Those skilled in the art also recognized that thiamine was a valuable meat flavoring precursor. Indeed, "[s]everal patents stress[ed] the importance of thiamin as a meat flavor precursor." EX1024(MacLeod), 409; *see also id.*, 400-07 & Table 17 (entries 12, 14, 19, 23, 29-31, 37, 45, 54, 61, 63, and 70). It was discovered that when thiamine was "heated in aqueous system with protein and a sulfur-containing compound(s), meat-like flavors [were] obtained." *Id.*, 409.

78. Other studies showed that in some cases methionine may be associated with meat-like flavors, such as pork flavor. *Id.*, 411 ("Methionine is the preferred amino acid for pork flavor.").

3. Use of Heme-Containing Proteins to Simulate Meat-like Characteristics

79. Well before 2012, the technical literature (e.g., patents and patent publications) touted that heme-containing proteins improved the meat flavor of a consumable. For example, as early as the 1980s, food scientists preparing meat replacement products added hemoglobin to improve the meat replacement products' meaty flavor and also provide a reddish, meat like color. U.S. Patent No. 4,818,557 ("Conrad") discloses that "[t]he addition of blood/hemoglobin further gives a desired taste improvement as it ***improves the meat flavour*** of the final product." EX1013(Conrad), 4:14-16. Conrad also teaches that "***colour*** [of "wheat meat"] can advantageously be ***transferred into meat colour by adding thereto up to 15% by weight of blood.*** EX1013(Conrad), 4:3-10. Conrad also teaches that the hemoglobin added should be isolated: "***preferably the hemoglobin part [is] separated off from blood***, the protein content of which is about 90% by weight and the dry substance contents are 33% by weight." *Id.*, 4:7-10. The hemoglobin added preferably makes up about 4-6% of the final product by weight. *See id.*, 1:56-61 (teaching meat replicas "compris[ing] the hemoglobin part of whole blood from slaughtered animals, preferably in an amount of up to 10% by weight dry weight of the gluten-

bran product dry weight, ***preferably 4-6% by weight***"); 4:32-44 (Table 2 disclosing a 2,100 g final product comprising 100 g hemoglobin, or about 4.8% by dry weight).

80. As another example, U.S. Patent Pub. No. 2008/0026128 ("Yamaguchi") discloses a process for improving the "body"/"rich" taste of foods, such as pork cutlet and pork dumplings. EX1022(Yamaguchi), [0023], [0029]. Yamaguchi explained that "a body taste-improving effect may be [] improved by adding a body taste-increasing component such as [] an iron component" to "the body taste improver." *Id.*, [0027], [0031]. This iron component may be "heme iron" or "blood cell powder." *Id.*, [0033]. International Publication No. WO 2013/010042 ("Brown") also expressly teaches that adding leghemoglobin to a flavor composition to be used in a meat substitute product provides an improved cooked meat aroma. *See, e.g.*, EX1012(Brown), [00364].

VI. THE '816 PROVISIONAL DOES NOT ADEQUATELY DESCRIBE THE CHALLENGED CLAIMS

81. As discussed further below, it is my opinion that the '816 Provisional does not adequately describe the Challenged Claims. In forming my opinion, I have adopted the following definition of a person of ordinary skill in the relevant art for the Challenged Patents.

A. POSITA Definition

82. The Challenged Patents are directed to the art of food science. I understand that Dr. Rodrigo Tarté has opined that a POSITA for the Challenged

Patents would have a Bachelor of Science degree in food sciences, biology, chemistry, microbiology, or a related discipline. A POSITA would also have a Master's degree or Ph.D. in food science or at least three years of experience working as a food scientist. A POSITA could also be part of a team of food scientists, including flavor chemists.

83. I agree with Dr. Tarté's definition of a POSITA for the Challenged Patents.

B. The Challenged Patents

84. I have reviewed the Challenged Patents. Claim 1 from each patent is reproduced below. As shown below, these claims recite "the production of at least two volatile compounds" that are "associated with" either a "meat-associated" ('096,'241 patents) or "beef-like" aroma ('306, '250 patents).

1. '096 Patent

85. Claim 1 of the '096 patent recites:

> A food flavor additive composition comprising:
> a) an isolated heme-containing protein;
> b) a compound selected from glucose, ribose, fructose, lactose, xylose, arabinose, glucose-6-phosphate, maltose, maltodextrin, and galactose, and mixtures of two or more thereof; and
> c) a compound selected from cysteine, cystine, thiamine, methionine, and mixtures of two or more thereof;

wherein the flavor additive composition contains no animal products; and

wherein cooking the food flavor additive composition results in the production of at least two volatile compounds which have a meat-associated aroma.

86. Claim 10

A food flavor additive composition prepared by a process of:

a) combining an isolated heme-containing protein;

a compound selected from glucose, ribose, fructose, lactose, xylose, arabinose, glucose-6-phosphate, maltose and galactose, and mixtures of two or more thereof; and

a compound selected from cysteine, cystine, thiamine, methionine, and mixtures of two or more thereof, to form a heme flavor reaction mixture, and

b) heating the heme flavor reaction mixture to at least 150° C. for at least 1 minute to result in the food flavor additive composition;

wherein the food flavoring additive composition contains no animal products; and

wherein the heme flavor reaction mixture has a meaty flavor and/or meaty aroma during the heating of step b) and the food flavoring additive composition has a meaty flavor and/or meaty aroma after the heating of step b).

2. ’306 Patent

87. Claim 1 of the ’306 patent recites:

A method for imparting a beef-like aroma to a meat replica matrix, wherein the meat replica matrix comprises one or more plant proteins,

a sugar selected from glucose, ribose, sucrose, fructose, xylose, maltodextrin, and combinations thereof, and at least one sulfur compound selected from methionine, cysteine and thiamine, the method comprising adding 0.01%-5% (by weight of the meat replica matrix) of a non-animal heme-containing protein to the meat replica matrix, wherein, upon cooking of the meat replica matrix, at least two volatile compounds are generated that are associated with a beef-like aroma, thereby imparting a beef-like aroma to the meat replica matrix.

3. ’250 Patent

88. Claim 1 of the ’250 patent recites:

A meat replica matrix comprising:
one or more plant proteins;
a sugar selected from glucose, ribose, sucrose, fructose, xylose, maltodextrin, and combinations thereof;
at least one sulfur compound selected from methionine, cysteine, and thiamine; and
0.01%-5% (by weight of the meat replica matrix) of a non-animal heme-containing protein,
wherein, upon cooking of the meat replica matrix, at least two volatile compounds are generated that are associated with a beef-like aroma.

4. ’241 Patent

89. Claim 1 of the ’241 patent recites:

A meat-like-food product produced by a method comprising:
providing one or more plant proteins; and
combining, with the one or more plant proteins:

a composition comprising a heme-containing protein, wherein the composition comprises at least 60% of the heme-containing protein on a dry weight basis;

a compound selected from glucose, ribose, fructose, lactose, xylose, arabinose, glucose-6-phosphate, maltose, and galactose, and mixtures of two or more thereof; and

a compound selected from cysteine, cystine, thiamine, methionine, and mixtures of two or more thereof in a concentration of at least 1.5 mM;

wherein the meat-like food product is free of animal heme-containing protein;

wherein cooking the meat-like-food-product results in the production of at least two volatile compounds which have a meat-associated aroma; and

wherein the meat-like food product is in a form selected from the group consisting of a hotdog, a burger, ground meat, a sausage, a steak, a filet, a roast, a meatball, a meatloaf, or bacon.

C. The ’816 Provisional

90. I understand and am informed that the Challenged Patents purport to “claim priority” to the ’816 Provisional, but that such a priority claim is only proper if, among other things, the ’816 Provisional’s disclosure adequately describes the later-issued claims. Based on my review of the ’816 Provisional, for multiple reasons set forth below, it is my opinion that the disclosure of the ’816 Provisional fails to adequately describe the full scope of the Challenged Claims.

91. I understand that for a patent claim to be entitled to the effective filing date of an earlier-filed patent application, the earlier application must provide adequate support and enablement for the claimed subject matter of the later-filed application. With regards to support, I understand that the U.S. Court of Appeals for the Federal Circuit held in the case of *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985), that "[t]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Accordingly, I understand that for the Challenged Patents, respectively, to be entitled to the filing date of the '816 Provisional application, the '816 Provisional's written description must have disclosed to a POSITA that on the date the provisional was filed, Patent Owner was in possession of the inventions claimed in the Challenged Patents, respectively.

92. I further understand that to meet this support requirement, it is the specification itself—not information outside of the specification—that must demonstrate possession. Thus, I understand that a description that merely renders the claimed invention obvious does not satisfy the requirement to show possession of the invention for purposes of written description support. For the following reasons, it is my opinion that the '816 Provisional does not contain adequate written

description to show possession of the subject matter claimed in the ’096 and ’241 patents, respectively.

93. ***First***, for each of the claims, the ’816 Provisional does not disclose all of the ultimately-claimed sugar and sulfur compounds.

94. I note that the ’816 Provisional discusses sugars in several locations: e.g., paragraphs [00124] [00217], [00254], [00255]. Despite this disclosure, I observe that it does not disclose certain claimed **sugars**—e.g., glucose-6-phosphate and maltodextrin—which are recited in the independent claims of the ’096 patent (maltodextrin is also recited in, e.g., the independent claims of the ’306 and ’250 patents; glucose-6-phosphate is also recited in, e.g., the independent claims of the ’241 patent). It also does not disclose three **sulfur compounds**—cystine, thiamine, and methionine—which are recited in the independent claims of the ’096 patent and ’241 patent (thiamine and methionine are also recited in, e.g., the independent claims of the ’306 and ’250 patents).

95. If the named inventors of the Challenged Patents had invented and were in possession of methods for producing meaty aromas at the time of filing the ’816 Provisional, and the volatile compounds associated with those aromas, in my opinion, the ’816 Provisional should contain at least some information regarding the amount of the claimed sugar and sulfur-containing compounds needed to achieve the desired results. As an analogy, if a provisional described only the use of flour

and sugar to make a product, information about these ingredients' proportions would be needed in order to show possession of methods for making a cake versus making biscuits. However, the '816 Provisional does not disclose specific concentration ranges of any sugars and sulfur compounds, or their proportions, in order to achieve meaty aroma or associated volatiles.

96. Each of these claimed-but-not-disclosed sugar and sulfur compounds has a unique chemical structure that is different from the compounds that are disclosed in the '816 Provisional. In my experience, chemical structure can be significant because it affects the compounds' chemical reactivity. For example, 5-carbon sugars (e.g., ribose) are more reactive in the Maillard reaction than 6-carbon sugars (e.g., glucose). Compounds with slower reactivity may be less successful at achieving the desired aroma profile with limited cooking time constraints.

97. The '816 Provisional does not disclose each of these compounds or their structures, indicating that, as of the date of the '816 Provisional, the named inventors did not have possession of all of the claimed precursors or the concentrations for their use in achieving the desired aromas.

98. ***Second***, the '816 Provisional does not describe any particular combination(s) of the recited sugar and sulfur compounds (plus a heme-containing protein) in a manner that would result in the production of volatile compounds which have a meat-associated or beefy aroma upon cooking, as claimed. As I explain in

my discussion of the Maillard reaction above, a POSITA would understand that these compounds will chemically react upon cooking of the meat replica matrix to produce volatiles. However, the profile of volatiles produced via this chemical reaction will depend on various parameters such as cooking time, cooking temperature, pH, and moisture. The ’816 Provisional does not describe the conditions, including specific precursor combinations, needed to produce meaty aroma, as claimed.

99. As exemplified below, this teaching is necessary because of the complexity of the diverse volatile profile underlying meaty aroma and the myriad possible combinations of precursor ingredients and reaction conditions that could achieve it. Permutations in volatile profile resulting from substituting precursors in the context of the Maillard reaction are potentially limitless, and not all may impart a desired aroma.

100. Although the art taught methods for using the claimed sugar and sulfur-containing compounds to achieve meaty and beef-like aroma via the Maillard reaction, the ’816 Provisional’s disclosure does not inform a POSITA that the named inventors of the Challenged Patents were in possession of such methods, including for precursors that were later claimed in the Challenged Patents but not disclosed in the ’816 Provisional.

101. Rather, the ’816 Provisional’s disclosure of adding heme protein into foodstuffs is general, and made almost entirely without reference to combinations with *specific* sugar or sulfur compounds. *See, e.g.*, EX1025, [0023], [0032], [00217], [00288], [00290]. Only a *single* paragraph in the entire disclosure describes thermally reacting certain heme-containing proteins (specified in EX1025 at [00106] (Table 1)) with specific Maillard precursors, and, even then, that disclosure is limited to only cysteine and glucose. *Id.*, [00255]. Thus, the ’816 Provisional does not disclose combining heme-containing proteins generally or even those heme-containing proteins specified in Table 1 with (1) any sugars except glucose or (2) any sulfur compounds except cysteine. Moreover, in the single paragraph of the ’816 Provisional in which the heme-containing protein is heat-reacted with cysteine and glucose, this reaction is not described as producing aromas associated with red meat (e.g., beef):

> Under these conditions, cysteine and glucose alone or in the presence of iron salts such as ferrous glucanate [sp.: gluconate] produced a sulfurous, odor ***but addition of heme proteins*** reduced the sulfurous odor and ***replaced it with flavors including*** but not limited to ***chicken broth, burnt mushroom, molasses, and bread***.

Id., [00255].

102. Notably, this experiment refers to combining cysteine and glucose with "hemeproteins taken from the list of Table 1." *Id.* Table 1, reproduced below, contains multiple heme-containing proteins:

Table 1

Class	Name	Organism	Sequence	Peak Absorbance Wavelength (nm)*
Bacterial Hemoglobin	AaTgb	*Aquifex aeolicus*	MLSEETIRVIKSTVPLLKEHGTEITARMYELLFSK YPKTKELFAGASEEQPKKLANAIIAYATYIDRLEE LDNAISTIARSHVRRNVKPEHYPLVKECLLQAIEE VLNPGEEVLKAWEEAYDFLAKTLITLEKKLYSQP	413
	HGbI	*Methylacidi-philum infernorum*	MIDQKEKELIKESWKRIEPNKNEIGLLFYANLFKE EPTVSVLFQNPISSQSRKLMQVLGILVQGIDNLEG LIPTLQDLGRRHKQYGVVDSHYPLVGDCLLKSIQ EYLGQGFTEEAKAAWTKVYGIAAQVMTAE	412
Leg-hemoglobin	LGB2	*Glycine max*	MGAFTEKQEALVSSSFEAFKANIPQYSVVFYTSIL EKAPAAKDLFSFLSNGVDPSNPKLTGHAEKLFGL VRDSAGQLKANGTVVADAALGSIHAQKAITDPQ FVVVKEALLKTIKEAVGDKWSDELSSAWEVAYD ELAAAIKKAF	415
Non-symbiotic hemoglobin	HORvu GLB1	*Hordeum vulgare*	MSAAEGAVVFSEEKEALVLKSWAIMKKDSANLG LRFFLKIFEIAPSARQMFPFLRDSDVPLETNPKLKT HAVSVFVMTCEAAAQLRKAGKITVRETTLKRLG GTHLKYGVADGHFEVTRFALLETIKEALPADMW GPEMRNAWGEAYDQLVAAIKQEMKPAE	412
	AFB70892	*Vigna radiata*	MTTTLERGFTEEQEALVVKSWNVMKKNSGELGL KFFLKIFEIAPSAQKLFSFLRDSTVPLEQNPKLKPH AVSVFVMTCDSAVQLRKAGKVTVRESNLKKLG ATHFRTGVANEHFEVTKFALLETIKEAVPEMWSP AMKNAWGEAYDQLVDAIKYEMKPPSS	412

**Bos taurus* myoglobin peak absorbance wavelength is 415 nm.

As shown in the Lipman Declaration (discussed further below in Section VIII.F.6), Patent Owner's experimental data confirms that the identity of the heme-containing protein can affect the profile of volatiles produced upon cooking. Yet the '816 Provisional does not clarify the combination(s) of specific heme-containing proteins from Table 1 with Maillard precursors that result in particular aromas/flavors.

103. This lack of disclosure is significant because a POSITA would understand that different combination(s) of the compounds recited in the Challenged Claims could produce aroma and flavor profiles that differ from the sole combination of leghemoglobin, cysteine, and glucose disclosed in the ’816 Provisional. As explained further above (Section VI), a POSITA would understand that the volatile products of the Maillard reaction depend on various factors such as cooking temperature, pH, cooking time, moisture content, and the structural diversity of the Maillard precursor molecules in the foodstuff. In my experience, for example, if the precursors are not heated to a high enough temperature, the reaction will not occur in a timely fashion and the mixture of volatiles produced will be different. As explained in Chapter 9 of Reineccius:

> Different blends of reactants may be heated under a wide range of conditions (including solids content and pH) to create a wide range of flavorings….
>
> The time and temperature of heating strongly include the flavor character of the process flavoring. It is generally acknowledged that heating temperatures of ca. 100°C yield cooked or stewed meat flavors and temperatures of ca. 120°C produce roasted meat flavors….
>
> While the pH during heating is generally about 5.2, IOFI and FEMA guidelines state that pH should be between 3 and 8.

EX1034(Reineccius), 271.

104. This chapter provides an example of how varying precursors and reaction conditions can differentially affect the resulting aroma/flavor profiles (Table 9.3, reproduced below).

Roast Beef Type Flavor

HVP	Sodium guanylate
Malic acid	L-methionine
Xylose	Water
Reflux at 100°C for 2.5 h	

Chicken Type Flavor

L-cysteine HCl	Glycine HCl
Glucose	L-arabinose
Water	
Heated to 90–95°C for 2 h then adjust pH to 6.8 with NaOH	

Pork Type Flavor

L-Cysteine HCl	Wheat gluten hydrolysate
D-xylose	
Heat at reflux temperatures for 60 min	

Bacon Type Flavor

L-cysteine HCL	Thiamin HCL
Liquid soy hydrolysate	D-xylose
Smoke flavor	Bacon fat
Cook at reflux temperatures for 90 min	

105. Thus, the lack of disclosure for achieving the claimed volatiles and aromas is not remedied by the ’816 Provisional’s laundry list of potential components of the food flavor additive, including “amino acids, fats, peptides, nucleotides, organic acids, sulfur compounds, sugars and other carbohydrates,” that allegedly produce “the characteristic flavor and fragrance components” of meat. EX1025, [00254]; *see also id.*, [00217] (providing a long list of “other soluble non-protein substances” found in meat that the meat replica also has, including “organic

acids, sulfur compounds, nitrogenous compounds"). These passages fail to adequately describe the claimed sugar and sulfur compounds—e.g., methionine, thiamine, and cystine—because generalized references to "sugars" and "sulfur compounds" do nothing to inform a POSITA that the named inventors were in possession of the full scope of the *specific* sugar and sulfur compounds and other recited elements in the Challenged Claims, and the conditions (temperature, pH, cook time) under which they can be combined to achieve the desired aroma.

106. ***Third***, as prefaced above, the '816 Provisional does not disclose any combination of a genus of heme proteins, sugars, and sulfur compounds ***in the context of the claimed foodstuff(s)*** (e.g., a food flavor additive or meat-like-food product). Rather, the '816 Provisional's limited discussion of heating the combination of cysteine, glucose, and heme proteins is only in the context of a controlled experiment reacting these three isolated compounds, divorced from any application to a food flavor additive or meat-like-food product. A POSITA would understand that the milieu of the foodstuff could affect the Maillard reaction chemistry and resulting aroma of the product—e.g., depending on the foodstuff's pH and moisture content. Depending on the presence of other components, the Maillard reaction may favor the generation of compounds and development of flavors that are not meaty. This is exemplified in the '816 Provisional itself ([00255]), in which the disclosed reaction produces aromas of "burnt mushroom," "molasses," and "bread."

107. Relatedly, I observe that the ’816 Provisional discloses adding leghemoglobin and myoglobin to a “poultry composition” such as real chicken and evaluating meat aroma. EX1025, [0044], [00256], [00407]-[00408]. First, I note that the combination of heme-containing proteins and chicken does not produce volatile “impact compounds” for beef-like aroma. *Id.*, [00265]. The volatiles disclosed in paragraph 265 are products of lipid oxidation that do not significantly contribute aromas associated with red meat (e.g., beef).

108. Moreover, this disclosure does not inform a POSITA that the named inventors were in possession of methods of imparting a meat-associated aroma to meat replicas or meat-like-food product(s) that contain “one or more plant proteins,” or a food flavor additive that “contains no animal products” or “no animal heme-containing proteins.” The chemical composition of these foodstuffs will almost certainly be quite different from that of poultry, and therefore, as a POSITA would understand, heat treatment of heme-containing poultry would lead to a different volatile profile than in the claimed foodstuffs.

109. I am informed and understand that the purpose of the written description requirement is to prevent a patent applicant (e.g., the named inventors of the Challenged Patents) from later asserting that he invented that which he did not. To that end, one cannot “disclose a forest” in the original application, and then “later pick a tree out of the forest and say here is my invention.” Instead, to satisfy the

written description requirement, "blaze marks" directing the skilled artisan to that "tree" must be in the originally filed disclosure. As explained above, the '816 Provisional fails to provide such "blaze marks" regarding combinations of sugar and sulfur compounds that are claimed-but-not-disclosed. Even for the sugar and sulfur compounds disclosed in the '816 Provisional, the provisional's disclosure fails to provide "blaze marks" indicating specific combinations of these compounds with all heme proteins or even certain heme proteins, or the conditions under which their combination will produce at least two meaty/beef-like aroma-associated volatiles, or the claimed aroma(s).

110. Furthermore, I am informed and understand that it is not adequate to describe the claimed compounds for the purposes of patentability merely because it would have been ***obvious*** to use thiamine and/or methionine (for example)—which are not disclosed in the '816 Provisional—in place of cysteine based on the teachings of the prior art. Thus, even if the claimed combinations of sugar and sulfur compounds would have been obvious to use as precursors in the well-known Maillard reaction discussed above, that obviousness is not sufficient to show possession of the claimed subject matter as of the date of the '816 Provisional.

VII. A POSITA WOULD REASONABLY EXPECT SUCCESS ACHIEVING PRODUCTION OF VOLATILE COMPOUNDS

ASSOCIATED WITH BEEF-LIKE OR MEATY AROMA VIA THE MAILLARD REACTION

111. In my opinion, a POSITA would reasonably expect success in producing volatile compounds associated with beef-like or meaty aroma in a foodstuff such as a meat replica matrix, food flavor additive, or meat-like product by using the sugars and sulfur-containing compounds claimed in the Challenged Claims in the product. As explained above (Section V.B), these compounds are long known to be Maillard reaction precursors.

112. Heating these precursors (when cooking the product) naturally produces volatiles that have been associated with meaty/beefy aroma, such as the character-impact compounds MFT and MFT-MFT. *E.g.*, EX1017(Mottram). In particular, these volatiles result from thermally reacting (cooking) the Maillard precursors cysteine and ribose. (EX1032, Cerny & Davidek, *Formation of Aroma Compounds from Ribose and Cysteine during the Maillard Reaction*, 51 J. AGRIC. FOOD CHEM. 2714-21 (2003); EX1045, Hofmann & Schieberle, *Evaluation of the Key Odorants in a Thermally Treated Solution of Ribose and Cysteine by Aroma Extract Dilution Techniques*, 43 J. AGRIC. FOOD CHEM. 2187-2194 (1995); EX1049, Hofmann & Schieberle, *Quantitative Model Studies on the Effectiveness of Different Precursor Systems in the Formation of the Intense Food Odorants 2-Furfurylthiol and 2-Methyl-3-furanthiol*, 46 J. AGRIC. FOOD CHEM. 235-41 (1998).). MFT and MFT-MFT also result from thermally reacting cysteine, thiamine, and hydrolyzed

vegetable protein. EX1141(Evers), 187.[6] U.S. Patent No. 3,519,437 ("Giacino") discloses meat-flavored compositions that include, among other ingredients, cysteine, thiamine, and hydrolyzed vegetable protein. EX1015(Giacino), 3:3-25, 5:1-10. Thus, a POSITA would have understood at least based on Evers' teachings that heating a flavoring composition, such as Giacino's, which includes cysteine, thiamine, and hydrolyzed vegetable protein, would produce MFT and MFT-MFT.

113. As I explain above (Section V.B), pH, cooking time, cooking temperature, and the moisture content of a product are variables that were known before 2013 to affect the production of volatiles from the Maillard reaction. As a POSITA would have familiarity with food science literature, principles and techniques, (Section IV.A), only ordinary skill would have been needed to follow the teachings of the prior art and adjust the parameters above in order for a POSITA to achieve production of volatile compounds associated with a beef-like or meaty aroma. For example, Reineccius suggests that cooking certain precursors at a higher temperature, for a longer time period compared to other precursors, can achieve

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[6] Evers was cited in Buttery et al., *Thiamin Odor and Bis(2-methyl-3-furyl) Disulfide*, J. Agric. Food Chem. 674-76 (1984), which I cited in my 2011 article submitted as EX1031. Therefore, I would have been able to locate the Evers reference at least as of 2011 with the exercise of reasonable diligence.

"roast beef" flavor. EX1034(Reineccius), 272, Table 9.3 (Examples of Process Flavor Formulations and Processing).

114. These observations do not change my conclusions in Section VI above. I am informed and understand that, within the '816 Provisional, the named inventors of the Challenged Patents were required to demonstrate to a POSITA that they possessed the full scope of the claimed subject matter. As explained above, the '816 Provisional fails to show that the named inventors possessed such methods at the time of that Provisional's filing.

VIII. PATENT OWNER'S SUBMISSIONS DURING PROSECUTION OF THE CHALLENGED PATENTS DO NOT SHOW SURPRISING RESULTS

115. As discussed further below, it is my opinion that Patent Owner's submissions during prosecution of the Challenged Patents of certain declarations and technical documentation do not show surprising or unexpected results associated with the Challenged Patents' claims. It is also my opinion that certain statements made by Patent Owner's attorneys regarding these declarations and documentation are incorrect.

A. Reasons for Allowance

116. I have reviewed the prosecution history of the Challenged Patents. I understand Patent Owner cited the declarations and technical documentation

discussed below during the prosecution of all four patents in order to obtain their issuance.

1. ’306 and ’250 Patents

117. I am informed and understand that the ’306 and ’250 patents are part of the same patent family, and that the ’306 patent was prosecuted first.

118. **’306 patent:** During prosecution of the ’306 patent, the Examiner repeatedly found that it would be obvious to fortify meat replica products with iron-containing leghemoglobin. In the April 4, 2018 Notice of Allowance, the Examiner reiterated the obviousness of this combination (EX1148(’306 PH), 3267):

> While ***Proulx et al. provides motivation to include leghemoglobin in a foodstuff, including a structured plant protein product such as disclosed by Hseih et al***, the reference is silent with respect to the influence of heme-containing protein on beef associated flavor.

119. The Examiner also recognized that the Maillard reaction and claimed sugars and sulfur compounds were important for generating meat flavor (EX1148(’306 PH), 3268):

> Cerny et al. … teach that the ***Maillard reaction plays a substantial role in flavor generation during the cooking of meat***. Cerny et al. teach that besides, thiamine, ***the precursors ribose and cysteine are important for meat aroma and are consequently employed in the product of meat flavors***.

120. The Challenged Claims were allowed because the Examiner credited Patent Owner's characterization of certain experimental data and supporting affidavits proffered by Patent Owner showed "novel" results relevant to the patentability of the claims (EX1148('306 PH), 3268):

> While Cerny et al. disclose that mixtures of ribose and cysteine, when heated, are known to produce flavors associated with meat, ***Applicants have demonstrated that the combination*** of: (a) a heme-containing protein b) compound selected from glucose, ribose, fructose, sucrose, xylose, maltodextrin and combinations thereof; and (c) at least one sulfur compound selected from methionine, cysteine and thiamine ***produces novel*** (i.e., ***not produced in the absence of heme-containing protein***) ***volatile compounds*** associated with a meaty aroma upon heating.

121. In my opinion, as explained below, the Patent Owner's arguments and proffered evidence was incorrect or misleading, and the Examiner's allowance of the claims was erroneous.

122. **'250 patent**: From my review of the prosecution of the '250 patent, the Notice of Allowance for that patent recited the same conclusion as in the Notice of Allowance for the '306 patent:

> While Cerny et al. disclose that mixtures of ribose and cysteine, when heated, are known to produce flavors associated with meat, ***Applicants have demonstrated that the combination*** of: (a) a heme-containing protein b) compound selected from glucose, ribose, fructose, sucrose,

> xylose, maltodextrin and combinations thereof; and (c) at least one sulfur compound selected from methionine, cysteine and thiamine ***produces novel*** (i.e, ***not produced in the absence of heme-containing protein***) ***volatile compounds*** associated with a meaty aroma upon heating.

EX1149(’250 PH), 754.

2. ’096 and ’241 Patents

123. **’096 patent**: On April 14, 2017, the Examiner rejected the pending claims of the application that led to the ’096 patent as anticipated by various prior art references. EX1002(’096 PH), 173-85. In response, on July 14, 2017, Applicant submitted, among other things, the declarations and technical documentation discussed below and advocated for the allowance of the pending application in light of the alleged surprising and unexpected results described in the declarations. *See id.*, 219-39. On September 24, 2017, Applicant submitted a supplemental response to the April 14, 2017 Office Action. *Id.*, 943-62. The Examiner subsequently allowed the application on December 6, 2017. *Id.*, 1172-82.

124. **’241 patent**: It is my understanding that the declarations and technical documentation discussed below are also part of the ’241 patent’s prosecution history. EX1150(’241 PH), 1231-40, 1269-72.

B. A POSITA Would Not Be Discouraged from Adding a Heme Protein to a Meat Replica or Food Flavor Additive Composition

125. A POSITA would not be discouraged from adding heme-containing protein to a meat replica or food flavor additive composition to achieve the claimed inventions of the ’096, ’241, ’250, and ’306 patents.

126. For example, in its October 17, 2017 Remarks during the prosecution of the ’306 patent, Patent Owner asserted:

> A [POSITA] would have not had a reasonable expectation of success that inclusion of leghemoglobin in the meat analogs and alternatives of the cited prior art would have resulted in meat replicas having acceptable organoleptic properties.

EX1148(’306 PH), 2714-15.

> [G]iven such statements [in Proulx (2006) and Proulx Thesis], a skilled artisan would not have been motivated to include leghemoglobin in a ground beef-like food product with any reasonable expectation of success that the organoleptic properties of the ground beef-like food product would not be adversely affected.

Id., 2715.

> Indeed, a [POSITA] would understand that heme iron has in fact been associated in the art with oxidation and off-flavors in meat.… Contrary to the Examiner’s assertion, a skilled artisan likely would have avoided including heme in the claimed meat replica matrix.

Id.

> Given the above understanding in the art related to the likely negative effects of heme-containing proteins on organoleptic properties, including oxidation, rancidity, and the production of off-flavors, a [POSITA] would not have a reasonable expectation of success that including a heme-iron-containing protein in a ground beef-like food product would result in a ground beef-like food product having an acceptable organoleptic profile.

EX1148(’306 PH), 2716.

127. In support, Patent Owner relied on an excerpt of a declaration from its expert, Dr. Keith Cadwallader (EX1148(’306 PH), 2715-16, citing ¶11 of the Cadwallader Declaration):

> This is a significant discovery since a [POSITA] would not have anticipated that the inclusion of a heme protein would have any beneficial effect on flavor. In fact, iron, and specifically heme iron, has been most often associated with causing deleterious off-odor consequences in foods and especially meat products (Calkins, 2007).

128. I disagree with Patent Owner’s and Dr. Cadwallader’s assertions regarding a POSITA’s motivation to include a heme-containing protein in a meat replica.

129. ***First***, I disagree with Dr. Cadwallader’s characterization of the Calkins reference’s teachings. In fact, Calkins (2007) teaches that heme iron is not a good indicator of beef flavor attributes.

> In general, total iron was not a good indicator of beef flavor attributes.... Small correlations between liver-like flavor and myoglobin concentrations in beef were seen, while hemoglobin relationship to livery flavor was not significant (Yancey et al., 2006).

EX1028(Calkins), 70. I note that Calkins (2007) does not cite to Pearson & Gray (1983), which teaches that myoglobin/heme-containing protein is not the catalyst of lipid oxidation in cooked meat, but rather Fe^{2+} which is released as the myoglobin/heme-containing protein breaks down. *See* EX1048(Pearson).

130. ***Second***, a POSITA would understand from the technical literature, such as Conrad (U.S. Patent No. 4,818,557, EX1013) and Yamaguchi (U.S. Patent Publication No. 2008/0026128, EX1022), that heme-containing proteins can contribute positively to food flavor and confer meaty flavor to a product, among other meat-like attributes such as coloration and nutrition profile (by virtue of containing iron). *See supra* Section V.D.3. For example, I see that Conrad states:

> The colour can advantageously be transferred into meat colour by adding thereto up to 15% by weight of blood …. ***The addition of blood/hemoglobin further gives a desired taste improvement as it improves the meat flavour of the final product.***

EX1013(Conrad), 4:5-16. This is consistent with my technical knowledge of the flavor chemistry (which includes aroma) of hemoglobin and other heme-containing proteins.

131. Yamaguchi discusses methods of achieving a "body taste," or "rich taste." EX1022(Yamaguchi), [0001], [0057]. Yamaguchi provides that "heme iron" and "blood cell powder" are "iron component[s]" (*id*., [0033]) which may "further improve[]" a "body taste-improving effect" from long-chain highly unsaturated fatty acids or their esters—i.e., oils used in cooking—for certain products. EX1022(Yamaguchi), [0031]. A POSITA would understand Yamaguchi's teaching to apply to meat replicas, as a POSITA would understand that a "rich taste" would be desirable to replicate savory and meaty flavors. Yamaguchi also discusses sensory evaluations of supplementing certain kinds of foods with iron. These experiments are discussed generally in Yamaguchi between paragraphs [0062] and [0101]. Yamaguchi explains its results as follows:

> In the sensory test, the improvement of body taste refers to the increase of "strength of aroma", "strength of flavour", "strength of taste" and "strength of aftertaste" without any deterioration of "goodness of aroma", "goodness of flavour", "goodness of taste" and "goodness of aftertaste", respectively.

EX1022(Yamaguchi), [0062]. Tables 5 and 6 of Yamaguchi are reproduced below.

TABLE 5

	Preparation oil (body taste improver)					
	(1)	(2)	(3)	(4)	(5)	(6)
AA concentration at an eating time (ppm)	10	10	10	10	10	10
Fe concentration in oil (ppm)	0	0.1	0.5	10	100	200

Strength of aroma	—	Δ	○	◎	◎	◎
Goodness of aroma	—	○	○	◎	○	Δ
Strength of flavor	—	Δ	○	◎	◎	◎
Goodness of flavor	—	○	○	○	○	Δ
Strength of taste	—	Δ	○	◎	◎	◎
Goodness of taste	—	○	○	◎	○	Δ

TABLE 6

	Preparation oil (body taste improver)					
	(1)	(2)	(3)	(4)	(5)	(6)
AA concentration at an eating time (ppm)	20	20	20	20	20	20
Fe concentration (ppm)	0	0.06	0.56	5.6	56	280
Strength of aroma	—	Δ	○	◎	◎	◎
Goodness of aroma	—	○	○	◎	○	Δ
Strength of flavor	—	Δ	○	◎	◎	◎
Goodness of flavor	—	○	○	○	○	Δ
Strength of taste	—	Δ	○	◎	◎	◎
Goodness of taste	—	○	◎	○	○	Δ

Yamaguchi concludes that, for both sets of experiments described in Tables 5 and 6, the results "show that all the strength of aroma, flavor and taste was increased by the existence of ***Fe component*** in the preparation oil … compared with … control"—i.e., iron. EX1022(Yamaguchi), [0093], [0101]. Accordingly, Yamaguchi teaches that iron, including heme iron, contributes positively to savory flavors, which would be desirable in meat replica products. This is also consistent with my technical knowledge of the flavor chemistry involving heme-containing proteins.

132. ***Third***, meat contains heme-containing proteins—notably myoglobin and hemoglobin—which, as discussed below, naturally contribute to oxidation of lipids present in meat in a positive manner. In fact, meat remains a widely-consumed and popular food despite such oxidation.

133. A POSITA would recognize that, over time, heme-catalyzed oxidation could produce undesirable flavor. But, for several reasons, this would not discourage a POSITA from incorporating heme-containing proteins naturally present in meat—either genetically engineered versions, or plant-derived equivalents—into a meat replica. ***First,*** the meat replica would likely be consumed shortly after cooking, before detectable undesirable flavors have time to develop. ***Second***, a POSITA could mitigate undesired oxidation by adding antioxidants to the meat replica. Indeed, U.S. Patent Publication No. 2008/0268112 ("Rolan") teaches adding antioxidants "to increase the shelf-life" of its meat replicas. EX1021(Rolan), [0038].

134. Patent Owner's and Dr. Cadwallader's assertions also oversimplify the relationship of lipid oxidation to meaty flavor. In fact, the art taught that lipid oxidation contributes positively to meaty flavor. Mottram teaches, for example:

> Phospholipids … contain a much higher proportion of unsaturated fatty acids than the triglycerides, including significant amounts of polyunsaturated fatty acids …. This makes them more susceptible to oxidation during heating and they have been associated with the off-flavour, known as 'warmed-over flavour', which develops in re-heated cooked meats (Pearson et al., 1977). However, they may also provide ***lipid oxidation products during the initial cooking of meat which contribute to desirable aromas***.

EX1017(Mottram), 420.

135. Yamaguchi also teaches or suggests a benefit to flavor associated with oxidation of fatty acids (which are components of lipids):

> A long-chain highly unsaturated fatty acid … has been considered for a long time a causative agent of putrefactive smell of meat and the like and off-flavor. However, it was found that ***when foods are mixed with the long-chain highly unsaturated fatty acid*** … alone ***or are subjected to oxidization treatment … the body taste of the foods will be improved and the original tastes of the foods will be increased***.

EX1022(Yamaguchi), [0026] (citation omitted).

> There is no limitation on the kind or structure of the body taste-increasing component, which includes as its representative examples … the iron component. Although ***it should not be construed to constrain the present invention in any way***, … the iron component [is] known to accelerate oxidization of fat and oil.

Id., [0032].

136. Thus, it is inaccurate and an oversimplification to assert, as Patent Owner and Dr. Cadwallader do, that lipid oxidation exerts a negative impact on meaty aroma and flavor.

137. Rather, undesirable flavors will develop in meat from lipid oxidation ***over time***. As explained in Pearson and Gray:

> The term "warmed-over flavor" (WOF) was coined … to describe the rapid development of oxidized flavor of cooked meat ***upon subsequent***

> ***holding***. The rancid or stale flavor becomes readily apparent ***within 48 h*** ....

EX1048(Pearson), 287. In my experience, and in my opinion, this would not discourage a POSITA from including heme-containing protein in a meat replica prior to cooking. Heme-containing proteins are naturally present in meat and, by virtue of their presence in meat, naturally contribute to its desirable flavor. Moreover, as Pearson and Gray explain, heme iron-mediated catalysis of negative flavors is triggered by cooking the product, which denatures the heme-protein and releases the iron from the porphyrin ring, thereby triggering the development of undesirable flavors detectable 48 hours later.

> Results demonstrate that Mb [myoglobin] per se is not the catalyst of lipid oxidation in cooked meat. However, ***cooking destroys part of the Mb, releasing Fe^{2+}*** which then catalyzes the development of WOF.

Id., 292. Thus, a POSITA would not expect heme-containing protein to exert a negative sensory impact in the product before it is cooked, and then not until days later.

138. It is feasible to slow down lipid oxidation. For example, Maillard reaction products—contributed by heat-reacting the claimed sugars and sulfur compounds—can slow down lipid oxidation due to their antioxidant properties when cooked at high heat.

> Certain products of the Maillard reaction are known to have antioxidant properties and are produced during retorting of meat.... [A] temperature of about 90 °C is required to produce the browning compounds responsible for the antioxidant activity in cooked meat.... [T]here was a relationship between antioxidant activity and development of the brown color …. [***T***]***he strong inhibitory action of the Maillard reaction products against WOF suggests that they could be useful in preventing development of WOF*** ….

EX1048(Pearson), 297-98. Thus, for example, the combination of the claimed sugars and sulfur compounds in a meat replica could slow down lipid oxidation catalyzed by the presence of a heme-containing protein. Other antioxidants in the product could have a similar effect. *Id.*, 298 ("A great deal has been written about the primary antioxidants, which may be used to inhibit development of WOF.").

C. The Challenged Patents Do Not Show Surprising or Unexpected Results

139. Based on my review of the '096, '241, '306, and '250 patents, they do not show that using heme-containing proteins in meat replicas or food flavor additive compositions leads to surprising or unexpected results.

140. In its October 17, 2017 Remarks (EX1148('306 PH), 2716-20), for example, Patent Owner pointed the Examiner to several portions of the '306 patent specification—Examples 16, 17, and 33—as support for advantages of aroma(s) produced by the claimed methods. I disagree with Patent Owner's assertions as explained below.

141. **Example 33.** Regarding Example 33, Patent Owner asserted (EX1148('306 PH), 2717):

> The present disclosure overcomes the organoleptic deficiencies of current meat analogs and meat alternatives and provides a consumable product (i.e., containing a meat replica matrix) that more accurately mimics the aroma of beef; see, e.g., Example 33 … which describes the production of beef flavors and aromas in replica burgers with the addition of heme and flavor precursors.

142. I disagree with Patent Owner's characterization of the specification. Example 33 does not show that ***adding heme-containing protein*** makes any beef-like aroma "more accurate." As taught in the patent, each replica in Example 33 contains heme-containing protein. '306 patent, 84:12-15 ("Flavor precursors along with 1% leghemoglobin were added to the ... burger replicas as indicated in Table 8."). Thus, Example 33 does not disclose the use of a "negative control" replica that does not contain heme-containing protein. A negative control would permit a more scientific comparison of aromas due to the presence of heme-containing protein.

143. The data in Tables 8 and 9 of the '306 patent, reproduced below, do not show a "more accurate" beef-like aroma. The sensory data for "Flavor Quality" show, for example, that beef has a score of 7.0 whereas the replicas have scores ranging from 3.2 to 4.3. The sensory data for "Flavor: Beef-like" show that beef has a score of 5.8 whereas the replicas have scores ranging from 2.3 to 4.2. In my

experience, such data do not show that any replica's aroma "accurately" or convincingly replicates the aroma of beef.

TABLE 8

Flavor precursors added to the beef replicas before cooking.

	Samples		
Additive (mm)	767 Precursor Mix 1	804 No Precursors	929 Precursor Mix 2
Alanine	5.61		5.61
Cysteine	0.83		0.83
Glutamic acid	3.40		3.40
Leucine	0.76		0.76
Lysine	0.68		0.68
Methionine	0.67		0.67
Tryptophan	0.49		0.49
Tyrosine	0.55		0.55
Valine	0.85		0.85
Glucose	5.55		5.55
Ribose	6.66		6.66
Lactic acid	1.00		1.00
creatine	1.00		1.00
Thiamine	0.50		0.50
IMP + GMP	0.40		0.40
Sucrose			2.00
Fructose			2.00
Xylose			2.00
Maltodextrin	0.50%		0.50%

TABLE 9

The sensory score determined by the sensory panel for the replica burgers and 80:20 beef sample.

			Sample #		
		Beef	767	804	929
Flavor Quality	mean	7.0	3.8	3.2	4.3
	STDEV	0.0	1.3	1.0	1.2
Flavor Intensity	mean	4.3	4.2	4.3	4.3
	STDEV	0.8	1.2	1.4	1.2
Flavor: Beefy	mean	5.8	3.3	2.3	4.2
	STDEV	1.0	1.2	0.8	1.2
Flavor: bloody/Metallic	mean	4.5	2.0	2.2	3.2
	STDEV	1.2	1.0	0.9	1.4
Flavor: Savory	mean	3.3	3.8	3.7	4.2
	STDEV	1.2	1.2	1.2	1.8
Off Flavors:	mean	1.5	2.3	3.5	2.7
chemical/oxidized/beany	STDEV	0.8	1.2	1.8	1.0

144. Moreover, Tables 8 and 9 show that different combinations and proportions of familiar Maillard precursors—not leghemoglobin—affects the sensory perception of meat replicas' aroma. For example, Sample 804, which has the lowest score on Table 9's "Flavor: Beefy" scale, did not include Maillard precursors (see Table 8). These proportions of precursors are not recited in the Challenged Claims, however.

145. Patent Owner also asserted (EX1148('306 PH), 2720):

> [T]he present application discloses the production of beef aroma-associated volatile compounds in the presence of LegH and the consequent generation of beef flavors in the presence of LegH are contained within the application as filed. See, for instance, Example 16 … Example 17 … and Example 33 ….

146. I disagree with Patent Owner's characterization of these disclosures. [A]s explained above, Example 33 has no negative control and therefore does not show that production of any volatiles results from the presence of leghemoglobin.

147. **Example 16.** Patent Owner's characterization of Example 16 is incorrect. Example 16, titled "Preparation of Meat Replicas in which the Particle Size of Individual Tissue Replica Units is Varied to Control Aroma Generation During Cooking," does not show that any volatile production—including volatiles associated with beef flavors—results from the presence of leghemoglobin. Nor does it show a "more accurate" beef-like aroma under any particular conditions. Indeed,

Example 16 discloses production of a variety of non-beef-like volatiles, including "aromas associated with store-bought gravy, faint citrus and star anise" (e.g., '306 patent, 72:15-17) and "soy sauce, musty, slightly rancid and beef bouillon" (*id.*, 72:21-23), and that "[a]ll samples … generated aromas associated with burnt meat smell" (*id.*, 72:25-27). These aromas, if anything, indicate production of aromas that are not associated with meat and less accurate and/or desirable.

148. Notably, the '306 patent disclosure teaches that differences in aroma relate to particle size: "the size of individual tissue units and the extent of their mixing … had profound effects on the generation of aromatic compounds upon cooking." *E.g.*, '306 patent, 72:28-31; 73:12-15, 26-28. This is consistent with my experience that variations in the internal environment or milieu of food products, such as meat replicas, can affect the flavors produced in that product.

149. **Example 17.** Patent Owner's characterization of Example 17 is misleading because that example purports to show the sensory effect from the combination of myoglobin and hemoglobin *with chicken*, which is not a meat replica matrix.

150. Results obtained using chicken would not necessarily be predictive of results obtained from cooking a meat replica product, as the chemical reactions involving plant proteins, plant fibers, and other ingredients in the replica product could affect its sensory profile. Natural chicken meat and a plant-based meat replica

are chemically different. Thus, heating a plant-based matrix containing heme-containing protein would be expected to yield a different volatile profile or flavor release (flavor within the matrix) than heating a chicken-based matrix containing heme-containing protein.

151. Even differences in the particle size and structure of foodstuffs can affect aroma production. For example, the ’306 patent (Example 16) provides examples of how a foodstuff’s other components can affect the generation of aromas.

> Sensory olfactory analysis of meat replica samples performed by a panel of testers, suggested that ***the size of individual tissue units and the extent of their mixing within meat tissue replicas correlated with generation of different aromas***.

’306 patent, 72:11-15.

> Furthermore, ***the levels to which all of the above compounds accumulated during cooking depended on the sizes of tissue units and how they are mixed*** (coarse particle size, fine particle size, or very fine particle size (blended)). Similar to meat tissue replica, it was found that ***structural organization and particle size of beef tissues modify response of beef tissues to cooking***.

Id., 72:52-59.

D. Patent Owner’s Proffered Experiments Do Not Show a Surprising “Beef-Like” Aroma

152. The Patent Owner was not able to overcome the Examiner’s grounds of rejection for the ’306 patent until the Patent Owner proffered experimental data and

declarations purporting to demonstrate production of "novel" beef aroma-associated volatiles under certain conditions. EX1148('306 PH), 2703-24. Relying on these experimental results, Patent Owner urged that the claimed methods of the '306 patent were non-obvious in light of the "surprisingly and unexpectedly improved organoleptic properties, including, in particular, the beef-associated aroma profile of the claimed meat replica matrix." *Id.*, 2717. Relying on many of the same declarations, Patent Owner made similar representations during prosecution of the '096 patent. EX1149('250 PH), 219-325. Patent Owner also submitted these declarations during prosecution of the '241 patent. EX1150('241 PH), 98-430.

153. In support, Patent Owner relied on certain statements from declarations of its employee, Celeste Holz-Schietinger, regarding experiments in which Maillard reaction precursors (e.g., ribose and cysteine) were heated either with or without leghemoglobin. I discuss these declarations further below. Regarding the Holz-Schietinger Declaration, for example, Patent Owner asserted:

> The surprisingly and unexpectedly improved organoleptic properties, including, in particular, the beef-associated aroma profile of the claimed meat replica matrix, are supported by the attached Declaration … by Dr. Celeste Holz-Schietinger [HSD] ….

EX1148('306 PH), 2717; *see also* EX1002('096 PH), 238.

> Significantly, as indicated in the [HSD], there were twenty-eight (28) different volatile compounds that were produced in the Ribose +

> Cysteine sample ***only when LegH was present***; these volatile compounds are indicated in Exhibit B as "Novel."

EX1148('306 PH), 2717 (emphasis in original); *see also* EX1002('096 PH), 237.

> Also as indicated in the [HSD], several volatile compounds were synergistically and dramatically increased in aqueous reaction mixtures of Ribose + Cysteine sample *only when LegH was present*.

EX1148('306 PH), 2719 (emphasis in original). For the '306, '250, and '241 patents, Patent Owner also relied on two other declarations by Dr. Holz-Schietinger which purportedly showed that, under similar conditions as the HSD, "at least two different volatile compounds that were produced … only when LegH was present … whose generation is attributable to the presence of the heme-containing protein [and] have been associated in the art, directly or indirectly, with a beef (or meat) aroma." *E.g.*, EX1148, 2720.

154. To bolster Dr. Holz-Schietinger's declarations, Patent Owner relied on statements by its experts, Drs. Cadwallader and Peterson, to argue that "each of the 28 volatile compounds" disclosed in the HSD "whose generation is attributable to the presence of the heme-containing protein have been associated in the art, directly or indirectly, with a beef (or meat) aroma." EX1148, 2718. For example:

> Among the 28 compounds identified in [HSD] experiments, two in particular are well-known to possess meaty sensory characteristics and to be important and potent odorants in cooked meat. Specifically, 2-methyl-3-furanthiol (MFT) and its dimerized form bis(2-methyl-3-

> furyl)disulfide (MFT-MFT) are important aroma compounds in cooked meat

Id. (citation omitted) (quoting Cadwallader Decl. ¶15).

> It is surprising to me that an intense meaty aroma compound such as MFT was uniquely identified in the reaction mixture upon the addition of LegH.

Id., 2718-19 (quoting Peterson Decl. ¶21).

155. I disagree that Patent Owner's proffered evidence supports its arguments.

156. As discussed below with respect to the Holz-Schietinger declaration(s), the profile of volatile compounds resulting from Patent Owner's heme protein-containing reactions (e.g., ribose/cysteine/leghemoglobin) differs to some extent from the volatile profile of the non-heme protein-containing reactions (e.g., ribose/cysteine). This is not surprising at least because, as a POSITA would recognize, changing the precursors of any chemical reaction will change the products that result from that reaction. Moreover, for multiple reasons explained below, Patent Owner's evidence does not show that the resulting aroma is "beef-like"—much less that it "more accurately mimics" the aroma of beef than the aroma produced from the non-heme protein containing reactions. Nor does it demonstrate surprising, unexpected, or novel production of volatile compounds. Nor still does it demonstrate that *heme-containing proteins* contribute to the development of meaty

aromas in a different manner than any other kind of protein would. Finally, as I discuss further below, there is no "nexus" between the evidence and the Challenged Claims to support secondary indicia of non-obviousness.

1. Failure to Include Sensory Evaluation

157. Patent Owner's tests, which are inadequately controlled, do not include a comparative sensory evaluation connecting any particular combination of volatile reaction products to the desired "beef-like" aroma. Patent Owner and its experts relied on literature teaching that certain compounds are associated with meaty aroma, but, without knowing the sensory impact of any particular profile of volatile components, the mere production of volatiles does not support finding that the resulting aroma would be perceived as "beef-like."

158. In my experience, sensory panels are necessary to determine whether a product's profile of volatiles achieves a particular aroma. Aroma results from sensory perception (specifically, the interaction of volatile compounds with olfactory receptors). Indeed, the term "organoleptic" means "affecting or involving an organ, esp. a sense organ."[7] Consistent with my experience, I note that Example 33 of the '306 patent discloses that "[t]hree replicas, … were cooked ***then served to a trained sensory panel to describe the flavor attributes*** shown in Table 9." '306

[7] *See* EX1113.

patent 84:15-18. Because the Patent Owner did not provide any actual organoleptic experimental data to the Examiner, however, Patent Owner's claim of "surprisingly and unexpectedly improved organoleptic properties, including, in particular, the beef-associated aroma profile of the claimed meat replica matrix" (EX1148('306 PH), 2717) is unsupported.

159. In my experience, for example, the presence of compounds such as methionine can, under certain conditions, result in flavor-significant levels of the volatile methional—the aroma of "boiled potato." EX1100(Ulrich), 111, 116. High levels of methional, e.g., in meat aromas (above its odor threshold) can overpower other aromas generated by Maillard volatiles.

> [T]he human sensory method employed here was effective in establishing sensory profiles of boiled potatoes…. Summarizing the results of both methods led to conclusions about essential aroma compounds. Methional … [was] recognized as [a] character impact compound[].

EX1100(Ulrich), 116. This complexity underscores the need to conduct sensory evaluations of product aromas.

160. Nor did Patent Owner provide adequate controls in these experiments. For example, these experiments do not contain data showing a true "beef-like" or meaty aroma to which the experimental reaction results could be compared. I would expect to see, for example, the production of volatiles from Patent Owner's

experiments in a side-by-side comparison with the volatiles produced by heated beef or other meat, with data explaining their relative levels in the aroma profile.

161. If any differences in aroma are due to the presence of *heme-containing protein*, I would also expect to see a control condition with another kind or form of protein, such as the globin portion of the heme-protein *without the heme ring or iron*. This control is necessary to show that any unexpected results are due to the presence of *heme-protein*, and not merely *any* kind of protein. For example, the Giacino reference shows how varying the amount and kind of "proteinaceous materials" in a compositions can yield different types of flavors.

> In general, ***development of a variety of flavors is achieved in separate compositions by providing in the premix, or in the reacted composition, a quantity of a source of one or more amino acids such as one or more free amino acids, proteinaceous materials, such as proteins, polypeptides and the like in which the amino acids are bound***, or the partial or complete hydrolysates or autolysates thereof, or in which the amino acids are partially or completely free.
>
> ***By varying the type and proportion of amino acid bearing materials this variety is conveniently obtained***. Generally, suitable results are obtained when the free amino acid, or mixture of free amino acids, or the proteinaceous material, or any combination of these are included preferably in the pre-mix, prior to reaction, but also in the reacted mix, at levels ranging up to about 50% by weight based on the total weight of the composition.

EX1015(Giacino), 2:52-68. However, Patent Owner's scientists did not use this control in their experiments.

2. Failure to Account for Meat Replica Composition

162. Patent Owner did not test the effect of including heme-containing proteins in the more complicated milieu of the claimed "meat replica matrix." Instead, Patent Owner's experiments tested volatiles from precursors and leghemoglobin heat-reacted in isolation (Dr. Peterson refers to these experimental conditions as "aqueous thermal reactions"). This approach does not support finding a surprising aroma in the ***claimed*** context of a meat replica matrix or meat-like product, which contain other ingredients such as plant proteins.

163. As explained further above, "beef-like aroma" is associated with hundreds of volatile compounds. *See supra* Section V.A. Yet, during prosecution, Patent Owner did not even attempt to account for the additional complexity of aroma produced following the heat-reaction of sugars, sulfur compounds, and heme proteins with many other kinds of molecules that may be present in its meat replica product—at minimum, the claimed "one or more plant proteins."

164. In fact, the combination of Maillard reactants and heme-containing protein with plant proteins and other components of a meat replica (e.g., lipids) could potentially lead to a non-"beef-like" volatile profile. As the '306 patent recognizes:

> Mixed meat tissue replicas can increase the sense of flavors … including … multiple aromatic compounds associated with

> fruity/grean[*sic*] bean/metallic, nutty/green, peanut butter/musty, raw potato/roasted/earthy, vinegary, spicy/caramel/almond, creamy, sweet, fruity/stale beer, musty/nutty/coumarin/licorice/walnut/bread, coconut/woody/sweet, penetrating/sickening, minty, or toasty caramel aromas.

'306 patent, 49:12-19.

165. Even Patent Owner's expert Dr. Devin Peterson recognized that "aqueous thermal reaction samples"—the conditions of Patent Owner's proffered experiments—"are simplistic compared to food matrices." *See, e.g.*, EX1148('306 PH), 2785.

166. Without sensory evaluation data from testing the claimed meat replica matrix—and even assuming Patent Owner's "novel" volatiles are even produced when a replica is heated (Patent Owner's experiments do not show this)—Patent Owner's conclusions are not factually supported. Accordingly, Patent Owner's limited data does not support the non-obviousness of a beef-like aroma produced within the context of the claimed meat replica matrix.

3. Increasing Volatile Levels Does Not Equate to Increased Beef-like Aroma

167. Patent Owner argued that increasing the levels of certain volatile compounds—purportedly achieved by only leghemoglobin—would translate into an improved beef-like aroma. I disagree. As noted above (Section V.A.1), increasing

the levels of aroma-associated volatiles—particularly character-impact compounds with low odor thresholds—can lead to an undesirable aroma.

168. A POSITA would therefore understand that merely increasing the amounts of certain compounds would ***not*** necessarily increase the desired aroma and could in fact affect it adversely. I have discussed this phenomenon in my own work. E.g., EX1031(McGorrin), 24. In the context of discussing meat flavor, Mottram similarly explains:

> [W]hen beef phospholipids were used the ***meaty aroma was more intense*** and the sulfurous notes less pronounced…. However, the phospholipid-containing reaction systems had ***lower concentrations of the meaty aroma compounds***, ***such as 2-methyl-3-furanthiol***. This anomaly may be explained in terms of a flavour-moderating role of the lipid. ***At high concentrations the furanthiol derivatives have strong, sulfurous odours***, ***and it is only at low concentrations that meaty aromas become apparent***. It is postulated that the lipid limits the production of these sulfur compounds and maintains their concentration at an optimum level in the reaction mixture. This hypothesis of flavour moderation and control may explain the particular role of phospholipids in the aroma of cooked meat.

EX1017(Mottram), 421.

> These meaty and nutty aromas are detected at low concentrations (<1 μg/kg), but at higher concentrations, the aromas are perceived as sulfurous and objectionable.

Id., 418; *see also* EX1119(Boelens), 32.

> Among the most important contributors to the characteristic aroma of cooked meat are 2-methyl-3-furanthiol, the corresponding thiophene, and disulfides derived from these thiols (Mottram, 1991). These compounds have extremely low odor threshold values, and consequently ***only trace amounts are needed for meatlike aromas; indeed, at higher concentrations many of the compounds become unpleasantly sulfurous in character***.

EX1129(Mottram), 987.

169. Thus, the concentrations of MFT reported in the Holz-Schietinger Declaration could translate to an unbalanced, unpleasant, sulfurous, non-meaty aroma. Without a sensory evaluation, it is impossible to know.

4. Patent Owner's Detected Volatiles Are Not Exclusively Associated with Beef-Like or Meat-Associated Aroma

170. As I discuss further above (Section V.A), the volatile components associated with beef-like or meaty aroma are complex and hundreds of compounds have been implicated in creating this sensory effect.

171. The purportedly "novel" compounds produced by the Patent Owner's leghemoglobin-containing reactions are ***not*** exclusively related to a meaty or beef-like aroma. Rather, as shown in the table below, these volatiles are also associated with the aromas or flavors of diverse foodstuffs such as fruits, coffee, wine, and grains. Additionally, 2-acetylthiazole and thiophene are not considered "impact compounds" for meat flavor.

172. In consequence, as a POSITA would understand, the presence of these compounds *alone* in a product is not necessarily associated with a meaty aroma. Rather, meaty or beef-like aroma results from the overall profile of volatiles, and their proportions in the aroma.

"Novel" Compound	**Aroma**
2-methyl-3-furanthiol (MFT)	• orange juice solutions containing thiamin hydrochloride[8] • Moutai (liquor)[9] • coffee and wheat bread[10]

[8] EX1043(Dreher), Abstract ("Both 2-methyl-3-furanthiol (MFT) and its dimer, bis(2−methyl−3−furyl) disulfide (MFT−MFT) were identified thus confirming that thiamin could serve as the precursor to these potent off-flavors in thermally degraded citrus juices.").

[9] EX1047(Zhu), 100038 ("Seven sulfur compounds … were detected in MT [Moutai, a Chinese liquour]. Noteworthy among these were 2-methyl-3-furanthiol (MFT … and bis(2-methyl-3-furyl) disulfide (MFT-MFT …), … which possess intense savory (meaty ***and vitamin-like***) aromas.").

[10] EX1051(Hofmann), 251 (reviewing literature) ("The thiols shown in Figure 1 [including MFT] are formed by the Maillard reaction of cysteine and might contribute to the flavors of heated foods and beverages, due to their low odor

"Novel" Compound	Aroma
bis(2-methyl-3-furyl) disulfide (MFT-MFT)	• orange juice solutions containing thiamin hydrochloride • Moutai (liquor) • coffee and black tea[11]
2-acetylthiazole	• wine • boiled and baked potatoes • rice bran[12] • nutty, cereal-like, popcorn-like[13]

thresholds. Actually, 2-methyl-3-furanthiol (MFT) … [has] been detected as [a] character impact odorant[] of roasted coffee … and wheat bread." (citations omitted)).

[11] EX1051(Hofmann), 251 (reviewing literature) ("The contribution of MFT-MFT to the flavor of roasted coffee and black tea has been suggested on the basis of aroma extract dilution analysis." (citations omitted)).

[12] EX1060(Marchand), 6160 ("2-Acetylthiazole has been found … in boiled and baked potatoes, and in rice bran…. The frequency of the occurrence of 2-acetylthiazole in wine is variable." (citations omitted)).

[13] EX1118(Wang), Abstract ("2-Acetylthiazole possesses a nutty, cereal-like and popcorn-like aroma … and this compound has been identified in some processed foods ….").

"Novel" Compound	Aroma
thiophene	• certain blackberries[14] • truffles[15]

5. No Nexus with Challenged Claims

173. I have been informed and understand that the asserted secondary considerations must have a "nexus" to the novel elements of the claim for the considerations to have any probative value as to obviousness.

174. Here, Patent Owner's proffered evidence of unexpected/surprising results does not have nexus to the novel aspects of the Challenged Claims. For example, as I explain elsewhere in my Declaration, there is nothing novel about using reducing sugars, such as glucose or ribose, and sulfur compounds, such as thiamine or cysteine, to produce beefy/meaty aromas. EX1032, Cerny & Davidek, *Formation of Aroma Compounds from Ribose and Cysteine during the Maillard Reaction*, 51 J. AGRIC. FOOD CHEM. 2714-21 (2003) (disclosing in detail the

[14] EX1056(Klesk), Abstract ("Evergreen blackberry aromas were analyzed by aroma extract dilution analysis…. [S]ulfur compounds (thiophene, …) were prominent in Evergreen.").

[15] EX1064(Splivallo), ("Truffles, [are] symbiotic fungi renown for the captivating aroma of their fruiting bodies …. [S]ulphur-containing volatiles such as thiophene derivatives, [are] characteristic of … fruiting bodies ….").

meaty/beefy aromas producing when reacting cysteine and ribose). Thus, the results of Patent Owner's experiments are merely in line with the teachings of the prior art (*see* Section V above); they do not represent a surprising or unexpected advance over those teachings.

175. Nor was it novel to use heme-containing protein to produce meaty flavors. EX1013(Conrad), 4:14-16 (disclosing that adding hemoglobin to a food product enhances "meaty flavour").

176. Moreover, nexus is lacking because, as I discuss above, Patent Owner has failed to show that the evidence demonstrates that the heme-containing protein is responsible for any alleged meaty/beefy aroma. *See* Sections VIII.C, VIII.D.1, VIII.D.3 above.

177. Additionally, Patent Owner fails to establish nexus at least because, as discussed further above, the evidence provided is not coextensive with the Challenged Claims. For example, Patent Owner did not test the effect of including heme-containing proteins in the more complicated setting of the claimed "meat replica matrix," but, rather, it tested volatiles from precursors and leghemoglobin heat-reacted in "aqueous thermal reactions"). *See* Section VIII.D.2 above. The Challenged Claims also recite specific flavor precursor compounds (*e.g.*, methionine, cystine, and/or thiamine, and certain reducing sugars) besides the limited precursors used in Patent Owner's experiments. *See* Sections VIII.F.1-3

above. Hence, the Challenged Claims broadly cover flavor precursor combinations (*e.g.*, methionine and xylose, or thiamine and fructose, etc.) that potentially do not even include the precursors or combinations thereof discussed in Patent Owner's experiments/declarations. For at least these reasons, Patent Owner fails to show nexus between its unexpected/surprising results considerations and the Challenged Claims.

E. Volatiles Produced in Patent Owner's Experiments Are Not "Novel"

178. Compounds that Patent Owner urged were produced ***exclusively*** with leghemoglobin—and which Patent Owner convinced the Examiner were "novel," as reflected in the Notice of Allowance for the '306 patent (EX1148('306 PH), 3258-69)—are, in fact, long known to be Maillard reaction products even in the absence of heme-containing proteins.

179. Both MFT and its disulfide MFT-MFT, which Patent Owner and its experts note "ha[s] been associated in the art … with a beef (or meat) aroma" (EX1148('306 PH), 2718), are produced from sugars and sulfur compounds via the Maillard reaction even in the absence of heme-containing proteins. For example, they are generated by thermally reacting ribose and cysteine:

> In reactions between cysteine, ribose, and lecithin under aqueous conditions a total of 152 compounds were identified …. In the previously reported aqueous systems, in the absence of lipid, the major

> volatile components were thiols such as 2-methyl-3-furanthiol [MFT] ….
>
> ******
>
> Among the most important contributors to the characteristic aroma of cooked meat are 2-methyl-3-furanthiol [MFT], the corresponding thiophene, and disulfides derived from these thiols (Mottram, 1991).... Such thiols were found in trace quantities in the four reaction systems ….

EX1129(Mottram), 985, 987 & Table 1.

> [E]xtract isolated from a thermally treated solution … of cysteine/ribose led to the identification of … 2-methyl-3-furanthiol [MFT] … and bis(2-methyl-3-furyl) disulfide [MFT-MFT] showing the highest flavor dilution factors among the 29 odor-active volatiles.

EX1045(Hofmann), Abstract.

> Thermal reactions of … cysteine/ribose mixtures were studied in model systems …. [G]eneration of [MFT] from cysteine/ribose mixtures was strongly enhanced ….

EX1093(Vauthey), Abstract. Calkins (2007), which Patent Owner cited to the Examiner (EX1148(’306 PH), 1966, 2069) also teaches that “[c]ysteine and ribose, through the Maillard reaction, as well as thiamin have been shown to create … [MFT]” EX1028(Calkins), 65 (citation omitted). And Cerny, cited by the Examiner, teaches “the formation of [MFT] from ribose and cysteine under the conditions studied.” EX1032(Cerny), 2718.

180. Similarly, 2-acetylthiazole and thiophene are produced by the Maillard reaction even in the absence of heme-containing protein.

> [A] … reaction of d-glucose and l-cysteine was constructed to investigate the formation pathway of 2-acetylthiazole.

EX1118(Wang) Abstract.

> The subsequent stages of the Maillard reaction …. lead to many important classes of flavour compounds including … ***thiophenes*** ….

EX1017(Mottram), 417.

181. Patent Owner may argue that leghemoglobin increases production of these volatile compounds; e.g., by acting as a catalyst. But, per Mottram (EX1017, 421) and others as explained above , ***merely increasing volatiles***—particularly meat "impact compounds" such as MFT—***does not increase meaty aroma***. In fact, increased volatiles can have an undesirable impact on aroma. Patent Owner's failure to conduct sensory evaluations that would help show whether or not increased levels of such volatiles actually translated to increased meaty aroma further underscores the lack of support for Patent Owner's position.

F. Declarations

182. Below, I summarize and comment on Patent Owner's proffered declarations.

1. "Holz-Schietinger Declaration"

183. I have reviewed the declaration of Dr. Celeste Holz-Schietinger ("Holz-Schietinger Declaration"). EX1148('306 PH), 2725-29. As discussed above, Patent Owner relied heavily on this declaration in seeking allowance of the pending claims of the '306 patent. This declaration was also submitted during prosecution of the '241, '250, and '096 patents. According to Patent Owner, Dr. Holz-Schietinger detected "novel" volatile compounds produced only from Maillard reaction precursors in the presence of leghemoglobin. EX1148('306 PH), 2727.

184. The Holz-Schietinger Declaration does not support Patent Owner's assertions for multiple reasons. As explained above, these compounds are known to be produced via the Maillard reaction even in the absence of leghemoglobin. *See supra* Sections V.B, V.D. Moreover, the disclosed experiments were not performed in the context of the claimed meat replica matrix. For example, the presence of other matrix components could affect which volatiles are produced, and in what proportions. Nor do they show the outcomes of reacting other claimed Maillard precursors besides ribose and cysteine, or proteins other than heme-proteins.

185. Additionally, the Holz-Schietinger Declaration does not disclose the use of a sensory evaluation to determine whether the resulting volatiles achieved a "beef-like" aroma. As I explain above, even meat aroma-associated compounds can be associated with other aromas as well. *See supra* VIII.D.4. Additionally, higher

levels of certain compounds, including MFT, can negatively affect meat aroma. *See supra* Section V.A.1; EX1031(McGorrin), 4; EX1017(Mottram), 418. Without such a test, the aroma of the volatiles cannot be conclusively determined.

186. I would also expect many more volatiles to be produced than are shown in the Holz-Schietinger Declaration's experiments (Exhibit B thereto), suggesting that the data have been selectively presented.

2. "Holz-Schietinger Heme Gradient Declaration"

187. I have reviewed the declaration of Dr. Celeste Holz-Schietinger described by Patent Owner as the "Holz-Schietinger Heme Gradient Declaration" (HSHGD) (EX1148('306 PH), 2802-11). According to Patent Owner, this declaration (EX1148('306 PH), 2720):

> describes flavor reactions mixtures (1) containing only Leghemoglobin (LegH) at different concentrations …; (2) containing a mixture representing the estimated concentrations of amino acids, sugars, and other small molecules in beef based on their values reported in literature ["Precursor Mix"] …; and (3) and containing both Leghemoglobin at different concentrations … and the Precursor Mix that have been cooked and then analyzed using GC-MS.
>
> Many different volatile compounds were produced, but the HSHGD focuses on those volatile compounds that have been associated in the art with a beef (or meat) aroma. Significantly, described in the HSHGD, there were at least two different volatile compounds that were produced in the Precursor Mixture sample only when LegH was present, i.e.,

volatile compounds whose generation is attributable to the presence of the heme-containing protein have been associated in the art, directly or indirectly, with a beef (or meat) aroma.

188. The Holz-Schietinger Heme Gradient Declaration does not support Patent Owner's assertions for multiple reasons. First, as explained above, these compounds are known to be produced via the Maillard reaction even in the absence of leghemoglobin. *See supra* Sections V.B, V.D. Second, the disclosed experiments were not performed in the context of the claimed meat replica matrix, but in an aqueous thermal reaction. For example, the presence of other matrix components could affect which volatiles are produced, and in what proportions.

189. Nor do these experiments contain the proper non-heme protein control. I see that Dr. Holz-Schietinger included leghemoglobin-only control condition(s) and a "precursor mix" containing amino acids (but not proteins). In my experience, however, the proper control for the effect of a *heme-protein* on the production of volatiles would be to use a control with the same protein structure (e.g., the globin protein) but lacking the heme ring/iron.

190. Additionally, the Holz-Schietinger Heme Gradient Declaration does not disclose the use of a sensory evaluation to determine whether the resulting volatiles achieved a "beef-like" aroma. As I explain above, even meat aroma-associated compounds can be associated with other aromas in other foodstuffs as

well. *See supra* Section VIII.D.4. Without such a test, the aroma of the volatiles cannot be conclusively determined.

191. I would also expect many more volatiles to be produced than are shown in the Holz-Schietinger Heme Gradient Declaration's experiments (Exhibit B thereto), suggesting that the data have been selectively presented.

3. "Holz-Schietinger Low Sulfur Declaration"

192. I have reviewed the declaration of Dr. Celeste Holz-Schietinger described by Patent Owner as the "Holz-Schietinger Low Sulfur Declaration" (HSLSD) (EX1148('306 PH), 2818-24). According to Patent Owner, this declaration (EX1148('306 PH), 2720-21):

> describes flavor reactions mixtures (1) containing only Leghemoglobin (LegH); (2) containing ribose and cysteine (ribose + 1.5 mM cysteine); and (3) containing Leghemoglobin with ribose and cysteine (LegH + ribose + 1.5 mM cysteine) that have been cooked and then analyzed using GC-MS.
>
> The [HSLSD] also describes flavor reactions mixtures (1) containing only Leghemoglobin (LegH); (2) containing ribose and thiamine (ribose + 1.5 mM thiamine); and (3) containing Leghemoglobin with ribose and thiamine (LegH + ribose + 1.5 mM thiamine) that have been cooked and then analyzed using GC-MS.
>
> Many different volatile compounds were produced, but the [HSLSD] focuses on those volatile compounds that have been associated in the art with a beef (or meat) aroma. Significantly, described in the [HSLSD], there were at least two different volatile compounds that

> were produced in the ribose and cysteine sample, or the ribose and thiamine sample, only when LegH was present, i.e., volatile compounds whose generation is attributable to the presence of the heme-containing protein have been associated in the art, directly or indirectly, with a beef (or meat) aroma.

193. The Holz-Schietinger Low Sulfur Declaration does not support Patent Owner's assertions for multiple reasons. First, these compounds are known to be produced via the Maillard reaction even in the absence of leghemoglobin. *See supra* Sections V.B, V.D. Second, the disclosed experiments were not performed in the context of the claimed meat replica matrix. For example, the presence of other matrix components could affect which volatiles are produced, and in what proportions. Nor do the experiments show the outcomes of reacting other Maillard precursors recited in the '306 patent claims besides ribose, thiamine, and cysteine. Nor do they contain a control protein condition (non-heme-protein).

194. Additionally, the Holz-Schietinger Low Sulfur Declaration does not disclose the use of a sensory evaluation to determine whether the resulting volatiles achieved a "beef-like" aroma. As I explain above, even meat aroma-associated compounds can be associated with other aromas in other foodstuffs as well. *See supra* Section VIII.D.4. Without such a test, the aroma of the volatiles cannot be conclusively determined.

195. I would also expect many more volatiles to be produced than are shown in the Holz-Schietinger Low Sulfur Declaration experiments (Exhibit B thereto), suggesting that the data have been selectively presented.

4. Declaration of Dr. Keith Cadwallader

196. I have reviewed the declaration of Dr. Keith Cadwallader. EX1148('306 PH), 2737-44. In this Declaration, Dr. Cadwallader comments on the Holz-Schietinger Declaration discussed above.

197. Dr. Cadwallader opines (¶14):

> It is my opinion that the above experimental approach and subsequent data analyses techniques used by Dr Celeste Holz-Schietinger are appropriate and acceptable for the purpose of evaluating and comparing aroma compound formation in the three reaction systems under heating conditions.
>
> It is also my opinion that these conditions which would simulate the cooking of a "ground beef-like food product" containing no animal products … and that the data obtained from the experimental approach would be reasonably predictive of the expected aroma compound formation from a "ground beef-like food product" containing no animal products and including the flavor reaction system components LegH, ribose, and cysteine.

198. I disagree. Regarding Dr. Cadwallader's first opinion, it is misleading insofar as it suggests that the HSD experiments can be extrapolated to the complex milieu of a meat replica matrix.

199. Regarding Dr. Cadwallader's second opinion, I disagree. As explained above, and as acknowledged in the '306 patent and elsewhere, a meat replica matrix is a complicated environment with many components. Heat-reacting a few isolated components does not adequately simulate the sensory outcome of cooking the replica or the latter's volatile profile. A POSITA would not be able to reasonably predict aroma compound formation, and its sensory impact, merely from reacting isolated components together.

200. Dr. Cadwallader opines (¶15): "Applicants' experiments … clearly demonstrate that inclusion of LegH in the reaction mixture has the surprising result of greatly enhancing the reaction of ribose and cysteine to form a variety of volatile compounds possessing meaty aromas."

201. I disagree. As explained above, no sensory data is shown for these experiments, and the presence of volatiles alone is insufficient to conclude that they result in a meaty aroma.

202. Dr. Cadwallader opines (¶16): "Applicants have indeed discovered and demonstrated the unique ability of heme-protein, including LegH, to serve as an efficient catalyst or promoter of the Maillard reaction and/or other relevant thermal reactions (e.g. thiamine degradation) which can form meaty aroma compounds in a 'ground beef-like food product' containing no animal products."

203. I disagree. As explained above, no sensory data is shown for these experiments, no non-heme-protein control is included, and the presence of volatiles alone is insufficient to conclude that they result in a meaty aroma. Moreover, a meat replica matrix is a complicated environment with many components. Heat-reacting a few isolated components does not adequately simulate the sensory outcome of cooking the replica or the latter's volatile profile.

204. Dr. Cadwallader opines (¶16): "a person having ordinary skill in the art would not have anticipated or expected this discovery based on the prior art cited." I disagree with this opinion insofar as it fails to account for the teachings of the prior art. Dr. Cadwallader's declaration does not consider, for example, Conrad or its teaching that "[t]he addition of blood/hemoglobin further gives a desired taste improvement as it improves the meat flavour of the final product." (Conrad, 4:14-16.) Nor does the declaration consider Yamaguchi or its sensory evaluation of iron supplementation on aroma of food products, which I discuss above. *See supra* ¶¶ 133-34, 138. Nor does Dr. Cadwallader's declaration explain why a POSITA would have a different expectation for a heme-containing protein native to plants, such as leghemoglobin.

5. Declaration of Dr. Devin Peterson

205. I have reviewed the declaration of Dr. Devin Peterson. *See, e.g.*, EX1148('306 PH), 2782-90. In his Declaration, Dr. Peterson comments on the Holz-Schietinger Declaration discussed above.

206. Dr. Peterson states that, among other things, "[i]t is my opinion that the experimental approach and subsequent data analysis techniques described in the Holz-Schietinger declaration are appropriate and acceptable for the purpose of evaluating and comparing aroma compound formation in the three aqueous thermal reaction systems under heating conditions." *Id.* ¶13. He further opines that this approach and methods are consistent with techniques used by POSITAs. *Id.*, ¶¶9, 17.

207. I note that Dr. Peterson's opinion in paragraph 13 is virtually identical to Dr. Cadwallader's opinion in paragraph 14 of the latter's declaration. As explained above for Dr. Cadwallader, in my opinion, Dr. Peterson's statements are misleading insofar as they suggest that the HSD experiments can be extrapolated to the complex milieu of a meat replica matrix.

208. Dr. Peterson further opines in paragraph 13, which is also virtually identical to Dr. Cadwallader's paragraph 14:

> It is also my opinion that these conditions which would simulate the cooking of a "ground beef-like food product" containing no animal products … and that the data obtained from the experimental approach

would be reasonably predictive of the expected aroma compound formation from a "ground beef-like food product" containing no animal products and including the flavor reaction system components LegH, ribose, and cysteine.

209. I disagree. As explained above, and as acknowledged in the '306 patent and elsewhere, a meat replica matrix is a complicated environment with many components. Heat-reacting a few isolated components does not adequately simulate the sensory outcome of cooking the replica or the latter's volatile profile. A POSITA would not be able to reasonably predict aroma compound formation, and its sensory impact, merely from reacting isolated components together.

210. Dr. Peterson states: "The different chemical classes of volatile compounds formed in the aqueous thermal reaction samples of the [HSD] are consistent with volatile aroma compounds reported in the literature evaluating volatile compound formation contributing to meat aroma and flavor sensation." *Id.*, ¶18.

211. In my opinion, Dr. Peterson's observation is not informative of the aroma of the HSD's reaction samples. It is true that certain compounds have been identified as associated with a meaty aroma. But it is not sufficient to say that, merely because a volatile compound is identified as present, the resulting *sensory* effect will be a meaty aroma. Meaty aroma—like the aroma of other foods—is

complex. As explained above, volatiles are associated with different, and often divergent, aromas of other foods.

212. Dr. Peterson opines: "In my opinion, Applicant's experiments in the [HSD] demonstrate that the addition of LegH to an aqueous thermal reaction mixture comprising ribose and cysteine has the surprising result of enhancing the formation of volatile compounds associate [*sic*] with a meaty aroma." *Id.*, ¶19.

213. In my opinion, this is misleading. As explained above, and taught in references authored by myself, Mottram, and others, the levels of volatiles alone does not necessarily predict the resulting aroma. As taught in Mottram (EX1017, 418), merely increasing the amount of meat aroma-associated compounds does not mean that the resulting aroma will be "meatier." In fact, undesirable sensory consequences can result. Moreover, it is not sufficient to say that, merely because a volatile compound is identified as present, the resulting *sensory* effect will be a meaty aroma. Meaty aroma is complex and, as explained above, volatiles are associated with different, and often divergent, aromas of other foods. Lastly, as noted, the experiments do not control for the effect of *heme-protein* as opposed to any other kind of protein.

214. Dr. Peterson states: "It is surprising to me that an intense meaty aroma compound such as MFT was uniquely identified in the reaction mixture upon the addition of LegH." EX1148('306 PH), 2789, ¶21.

215. I disagree. As explained above, MFT is a known Maillard reaction product. Moreover, this statement is misleading because, as noted above, it is not sufficient to say that, merely because a volatile compound is identified as present, the resulting *sensory* effect will be a meaty aroma. Meaty aroma is complex and volatiles are associated with different, and often divergent, aromas of other foods.

6. Declaration of Dr. David Lipman

216. I have reviewed the July 11, 2017 declaration of Dr. David Lipman (EX1148('306 PH), 2881-88), who I understand to be the Chief Scientific Officer of Impossible Foods. Patent Owner asserted (EX1148('306 PH), 2722):

> According to the Lipman Declaration, the ability of four very distinct members of heme-containing proteins to generate meat-associated volatile aroma compounds upon heating, coupled with the experimental data demonstrating that even heme unbound to protein (i.e., hemin) shared such meat aroma and flavor production properties when heated in a reaction mixture, make it likely that these functional properties are not based on protein sequence similarity, but are instead based on the commonality among the proteins and hemin, namely, the inclusion of the heme co-factor.

217. I disagree with Patent Owner's characterization of Dr. Lipman's declaration. The Lipman Declaration shows that, in fact, heat-reacting the Maillard precursors ribose and cysteine with different heme-containing proteins leads to the production of ***different*** volatile profiles. I reproduce below from the Lipman

Declaration a table of certain experimental results. *See, e.g.*, EX1148('306 PH), 2884-84, ¶14. According to Dr. Lipman, this table reflects certain volatiles produced from reacting 10 mM cysteine and 10 mM ribose with 10 mg/ml of four different heme-containing proteins: leghemoglobin (LegH), barley hemoglobin, bovine (cow) myoglobin, and an *A. aeolicus* heme-containing protein. *Id.*, ¶13. The table is generally organized such that compounds detected in most or all experiments appear at the top of the table, while the bottom of the table identifies compounds that do not appear in all experiments.

Name	LegH	Barley	*B. myoglobin*	*A. aeolicus*
Furan	x	x	x	x
Thiazole	x	x	x	x
benzaldehyde	x	x	x	x
2-acetylthiazole	x	x	x	x
2-methyl-propanal	x	x	x	x
furfural	x	x	x	x
2,3-butanedione	x	x	x	x
2-pentyl-furan	x	x	x	x
2-pentanone	x	x		
pyrazine	x	x	x	x
dimethyl trisulfide	x	x	x	x
3-methyl-butanal	x	x		x
2-methyl-thiazole	x	x	x	x
pentanal	x	x	x	x
1,3,5-cycloheptatriene	x	x	x	x
methacrolein	x	x	x	x
heptanal	x	x	x	x
2-methyl-butanal	x	x		x
isothiazole	x	x	x	x
thiophene	x	x	x	x

propanal	x	x	x	x
2-heptenal	x		x	x
methyl-pyrazine	x	x	x	x
1-octene	x		x	x
butanal	x	x	x	x
2-acetyl-propen-2-ol	x	x	x	x
pyrrole	x	x	x	x
2-methyl-furan	x	x	x	x
nonanal		x	x	x
2-propenal		x	x	x
2-decenal		x	x	x
2-nonanone		x		x
2-octanone		x	x	x
2-tridecen-1-ol,			x	x
2-octanone			x	
2-octenal			x	x
4-methyl-2-heptanone			x	x
octanal			x	x
2-undecenal				x
butyrolactone				x
1-octen-3-one				x
3-methylheptyl acetate				x
2-pentyl-thiophene				x

218. Although these volatile compounds may be associated with a meaty aroma, none in my experience are meat aroma "impact compounds," and I note that the table reproduced above does not identify the relative levels of these volatiles. I also note that, in my experience, certain of these volatiles are lipid byproducts, suggesting that the preparation of the purified proteins used in these reactions may contain byproducts of trace amounts of lipids or fats.

219. Moreover, Dr. Lipman's declaration suffers from the same deficiencies identified above for the Holz-Schietinger, Cadwallader, and Peterson declarations. The results described in the Lipman Declaration do not include any ***sensory*** evaluation of the volatile compounds produced in these experiments. As I explain

above, a meaty or beef-like aroma cannot be assumed from volatiles alone. Nor do Dr. Lipman's experiments include a *non-heme-protein* control condition.

G. No Other Secondary Considerations Support the Challenged Claims' Non-Obviousness

220. In my opinion, no other secondary considerations of non-obviousness support the Challenged Claims.

1. No Long Felt but Unmet Need, Skepticism, or Failure of Others

221. **Skepticism:** I am not aware of any skepticism in the field regarding the possibility of producing beef-like aromas in foodstuffs, including in plant-based products. As explained above in my Declaration, the Maillard reaction has long been used to produce volatile compounds associated with meaty, beef-like aromas from precursor compounds such as cysteine and ribose—a technique which has been used and studied in the food flavor industry for nearly 60 years. These techniques are disclosed in Mottram (EX1017) and other references cited herein. Moreover, the importance of lipid (fat) degradation (upon cooking) to meaty aroma has also long been understood (e.g., as disclosed in Mottram). There is also no nexus as to any alleged skepticism because I am unaware of any skepticism that adding heme-containing protein to a meat replica or flavoring composition would contribute to meaty aromas, particularly considering meat itself contains heme-containing proteins.

222. **Unmet Need/Failure of Others:** I am aware of an independent study by LiLi Zyzak, Nathaniel Britt, Callie Boggs, Phillip Gilbert, and Lucy Jones that evaluated the aromas associated with eight plant-based burgers including Patent Owner's burger product. I understand Dr. Zyzak, the principal investigator, is an Assistant Professor in the Department of Chemistry at Eastern Kentucky University.

223. Dr. Zyzak's study, titled "Investigation into the sensorial and analytical differences of traditional hamburgers versus the plant-based analogues," was presented on August 23, 2021 at the Fall National Meeting of the American Chemical Society (ACS) in the Division of Agricultural and Food Chemistry, in Atlanta, GA (August 22-26, 2021). I have attached a copy of the abstract I located on the ACS website received to this Declaration as EX1098.

224. I note that this abstract reports the results of both gas chromatography analysis-mass spectrometry (GC-MS) ***and*** sensory evaluations of these plant-based beef analogs' aromas—not merely the GC-MS results (EX1098, Abstract):

> Recently, there has been a surge in the development of these alternative meat products, especially in the hamburger area. These new prototypes are making significant progress in appearance and flavor; nonetheless, all of them have significant flavor differences from real hamburger aroma and flavor. ***This presentation will focus on identifying the sensorial and analytical differences between real hamburger and the leading plant-based prototypes in the marketplace. Correlations between sensorial and analytical*** will be discussed by leveraging Gas

> Chromatography – Mass Spectrometry – Olfactometry (GC-MS-O). Many of the plant-based prototypes have elevated roasted note compounds and lack the sweet, meaty, and fatty notes of traditional hamburgers. In addition, these plant-based prototypes are sometimes complemented with herbs or spices to add flavor.

225. I have reviewed other summaries and reports of the results of Dr. Zyzak's study. An August 23, 2021 ACS News Release titled "Sniffing out which plant-based burgers smell the most like real beef" reported (EX1114):

> The team then identified the compounds that caused the plant-based burgers to differ from traditional hamburger. Of the alternatives tested so far, ***the Beyond Burger from Beyond Meat most closely resembled the odor profile of actual hamburger, with meaty, fatty and grilled meat characteristics from the compounds 1-octen-3-ol, octanal and nonanal***; however, it was still significantly different from the real thing. ***Another brand had the closest appearance to real raw hamburger, but upon cooking, it had a yeast- or bread-like odor***, with higher levels of methyl butanals and propionic acid. A number of the other brands had heavy seasonings that released strong garlicky or barbecue-sauce-like aromas.

226. As another example, *Treehugger* magazine reported in a September 3, 2021 article titled "Science Reveals Which Plant-Based Burger Smells Closest to the Real Thing," that other burgers had an aroma profile after cooking that is closer to the aroma of a typical beef hamburger. *See* EX1115. Compared to burgers made by competitors Beyond Meat and Nestlé, Patent Owner's (Impossible Foods)

"Impossible" burger "gave off notes of yeast and grain," which, in my experience, are not typical aromas associated with cooked natural beef and would be undesirable in the aroma of a beef replica.

> According to the results of the research, ***cooked burgers from Beyond Meat most closely match the odor profile of real hamburger.*** That said, despite having characteristics of "meaty, fatty, and grilled meat," Zyzak noted that it was "significantly different" from the real thing. ***Coming in second place was Nestlé's Awesome Burger.***
>
> ***"I think Beyond's done a pretty good job at it, actually,"*** Zyzak told the National Post. ***"And the Awesome is really, really close to it in terms of the regular beef profile."***
>
> As for some of the other contenders, ***the odor of the Impossible Burger gave off notes of yeast and grain***, Kellogg's Incogmeato Burger produced a garlic aroma, and Simple Truth's Emerge smelled like sweet BBQ sauce.
>
> "We don't know all their trade secrets," Zyzak, laughing, added to the Post. "So we're trying to figure out, why would someone add that?"

227. It is my understanding that neither the "Beyond Burger" nor the Nestlé "Awesome" burger contain a non-animal heme-containing protein such as the leghemoglobin used in Patent Owner's "Impossible" burger. Accordingly, the advantageous aroma of these competitor burgers does not result from the presence of heme-containing protein (including "non-animal" heme-containing protein).

228. I have also listened to the study's lead author, Dr. LiLi Zyzak, describe her findings in a video of ACS Fall 2021 Media Briefings, available online at YouTube.com.[16] Dr. Zyzak explains that the improved aroma of the Beyond Burger is due to its fatty acids, canola and coconut oil, which are more similar to animal fatty acids, than the sunflower oil used in Impossible's product. Specifically, between the 15 and 17 minute marks in this video, Dr. Zyzak states:

> The trick is really the profile of the fatty acid. Okay, so, ***beef***, in general, ***has more what we call unsaturated 18-1***. Now, chicken would have more of 18-2…. So how do you mimic that fatty, meaty note? So ***canola oil*** … ***has the highest level of the 18-1***. And sunflower is about 20 percent, canola, I think, is about 60, 70 percent, something around there…. Sunflower is about 20, 30 percent. ***So if you look at Beyond, they use canola oil and coconut oil. Now, Impossible uses sunflower oil. So, it has a higher content of 18-2.*** So, I don't really know their reasoning for doing all that …. But, um, just looking at the data we have, ***I think that canola oil is going to be driving it closer to the real beef hamburger***, because it's a mixture, like I said it's not one compound that gives us the real hamburger aroma perception, it's a blend of everything … and that's the tricky part.

[16] EX1146, https://www.youtube.com/watch?v=3W_0GqGnsN4&list=PL-qHxGvFeZV1ofkLBQIgRN2ULEVedPnR-&index=12, last accessed Nov. 10, 2022.

229. Accordingly, it is my opinion that there is no "failure of others" in the field of food science to achieve a meaty or "beef-like" aroma in meat replica matrices or meat-like food products, or the production of volatile compounds associated with such aromas. As shown in Dr. Zyzak's study, such aromas are achievable using other conventional techniques (e.g., the selection of specific oils and other ingredients for use in the product). Similarly, there is no nexus between any alleged "failure of others" and the inclusion of heme-containing protein in meat replicas and flavoring compositions.

230. Nor, for the same reasons, is there a "long felt but unmet need" in the field for such aromas that Patent Owner's "Impossible" burger provides. Rather, the aromas of competitor burgers such as the Beyond Burger and Awesome Burger provide such desirable beef-like aromas.

2. No Nexus to Commercial Success

231. It is my understanding that the Patent Owner's commercial foodstuff products contain a "non-animal" heme-containing protein (leghemoglobin). I see, for example, that Patent Owner's website asserts:

> [W]e ***discovered that one molecule—heme—is primarily responsible for generating the*** … ***flavor and aroma of cooked meat.***
>
> *****
>
> When we mixed ***leghemoglobin*** with plant proteins, fats and other simple nutrients, it ***transformed*** … ***veggie burger into . . . meat***!

See EX1121, 2-3. I disagree with the Patent Owner's assertions, which I understand to be promotional and/or advertising. Rather, in my experience—and consistent with the teachings of Mottram and Dr. Zyzak's study—meaty, beef-like aroma is contributed by a variety of factors such as the volatile products of the Maillard reaction and lipid degradation. I am not aware of any data showing that any heme-containing protein produces such a cooked meat aroma.

232. Moreover, I understand that leghemoglobin in the Patent Owner's products does not have a different effect in a foodstuff than heme-proteins (e.g., myoglobin) that are naturally present in meat. I see, for example, that the Patent Owner admitted to the U.S. Food & Drug Administration that leghemoglobin is equivalent to other heme-containing proteins such as myoglobin. EX1052, 7 ("[A]nimal myoglobins, plant hemoglobins and plant leghemoglobins … are structurally very similar …."); 24 ("[T]here is no evidence to suggest that soy leghemoglobin in food will behave any differently from the myriad other functionally equivalent and widely consumed globin proteins in the human diet.").

233. I am informed and understand that a "nexus" between a product and a patent claim may be presumed when the product is "co-extensive" with the claim. I am informed and understand that a patent claim is not co-extensive with a product that includes a critical ***unclaimed*** feature that materially affects the product's functionality—e.g., an ingredient such as a fat or lipid in a foodstuff that is not

recited in any of the Challenged Claims. To the extent the aroma of Patent Owner's products derive from such unclaimed ingredients, I understand they are not "coextensive" with the Challenged Claims.

234. I am also informed and understand that evidence supporting secondary considerations of non-obviousness must be shown to have a "nexus" to the claimed invention. I am not aware of any evidence that shows a "nexus" between, e.g., the leghemoglobin in the Patent Owner's products and any commercial success of such products.

235. Rather, from my review of other materials, I understand that commercial success of the Patent Owner's products (assuming they are commercial embodiments of the Challenged Claims) derives from ***unclaimed*** factors such as Patent Owner's aggressive commercial strategy in the plant-based foodstuff market:

> [T]he majority of Impossible Food's initial partnerships …. were more resilient during the [COVID-19] pandemic, allowing Impossible to scale quickly and reduce costs.
>
> ******
>
> Impossible Food's rapid growth over the pandemic—hitting production records and achieving greater economies of scale—allowed them to drastically slash their prices by 20% in restaurants and grocery stores earlier this year in an attempt to better compete with meat. They made their product more buyable to the broader consumer base ….

EX1120, 4. I understand that the Patent Owner has also hired seasoned advertising consultants to "supercharge its marketing efforts," following its "intentionally aggressive ad campaign." EX1147, 1-2.

236. I am not aware of any evidence of other so-called "secondary considerations" of non-obviousness related to the Challenged Claims, assuming the Patent Owner's products are embodiments of these claims. I am informed and understand that it is the Patent Owner's burden to produce such evidence. I reserve the right to consider and respond to such evidence if produced by the Patent Owner.

IX. CONCLUSION

237. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

238. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on the information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: December 7, 2022

Dr. Robert McGorrin