SAFETY EVALUATION OF CULTURED CHICKEN CELLS PRODUCED BY BELIEVER MEATS

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List of Abbreviations

ACF	animal component free
ADI	acceptable daily intake
AOAC	Association of Official Analytical Collaboration
BSE	bovine spongiform encephalopathy
cGMP	current Good Manufacturing Practice
CIP	cleaning in place
COA	certificate of analysis
DO	dissolved oxygen
DV	Daily Value
EEE	Equine Encephalitis Viruses
EFSA	European Food Safety Authority
ELISA	enzyme-linked immunosorbent assay
ERP	Enterprise Resource Planning
FALCPA	Food Allergen Labelling and Consumer Protection Act
FASTER	Food Allergy Safety, Treatment, Education and Research Act
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
HARPC	Hazard Analysis and Risk-based Preventative Controls
HPAI	Highly Pathogenic Avian Influenza
HPLC	high-performance liquid chromatography
LOQ	limit of quantitation
MCB	master cell bank
MT-CYB	mitochondrially encoded cytochrome B gene
MWCB	manufacturer's working cell bank
MXNS	Merieux NutriSciences
ND	Newcastle Disease
NHANES	National Health and Nutrition Examination Survey
OIE	World Organization for Animal Health Office International des Epizooties
PQCI	Preventative Controls Qualified Individual
PD	population doubling
PRP	prerequisite plan
QA	quality assurance
qRT-PCR	quantitative real-time polymerase chain reaction
rGF	recombinant growth factor
SIP	sanitizing in place
SNV	single nucleotide variation
SOP	standard operating procedures
TPC	Total Plate Count
TSB	tryptic soy broth
TSE	transmissible spongiform encephalopathy
UL	Upper Level
USDA	United States Department of Agriculture
USP	United States Pharmacopeia
WHO	World Health Organization

Safety Evaluation of Cultured Chicken Cells Produced by Believer Meats

1.0 ADMINISTRATIVE DATA

Believer Meats Ltd. ("Believer Meats"; formerly known as "Future Meat Technologies") hereby provides notice to the United States (U.S.) Food and Drug Administration (FDA) of the company's conclusion that its cultured chicken cells are as safe as conventional meat derived from a chicken carcass. This document provides a summary of the basis for that conclusion and is submitted pursuant to the voluntary premarket safety consultation process established by the FDA for foods made with cultured animal cells.

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2.0 INTRODUCTION

Believer Meats, a company specializing in cultured meat production, has developed technology for the manufacture of meat products using cells isolated from livestock such as chickens, sheep, and cows. Believer Meats' meat products are cultivated in a nutrient-rich solution within bioreactors at high cell densities. Finished food products produced using this process are hereby referred to as "cultured chicken," "cultured meat," or "cultured poultry."

This submission describes the identity, large-scale production, and safety profile of **cultured chicken fibroblasts (synonym: cultured chicken cells)** produced from cells isolated from domestic chickens (*Gallus gallus domesticus*) without the use of recombinant DNA technology. The cells are grown in bioreactors and then harvested as a biomass of chicken cells that can be used alone or combined with commonly used plant-based ingredients (*e.g.*, textured plant protein) and extruded into finished products (*e.g.*, chicken breast). Cultured meat products produced from these cultured fibroblasts are similar to conventional meat products (*e.g.*, chicken breast) in their texture, nutritional composition, and safety profile. Information on the derivation and characterization of Believer Meats' cell lines used to make cultured chicken cells has been made available in a peer-reviewed publication by the Nature Publishing Group (Pasitka *et al.*, 2023).

Regulatory oversight of food products produced from cells of livestock is subject to the formal agreement established by the FDA and USDA-FSIS in March 2019 (U.S. FDA, 2020). Under this agreement the FDA oversees cell collection, cell banks, and cell growth and differentiation. Transition to oversight by the USDA-FSIS occurs at the point of harvesting the biomass. USDA-FSIS also oversees the further production and labeling of these products. As discussed in the formal agreement, the FDA's approach to regulating products derived from cultured animal cells involves a thorough pre-market consultation process and inspections of records and facilities as applicable. The data and information in this submission represents the outcome of discussions between Believer Meats and the FDA over a multi-year consultation period.

This submission outlines Believer Meats' step-by-step process for evaluation of the safety of its cultured chicken fibroblast cells. Believer Meats has identified a number of potential hazards and has enacted corresponding risk mitigation measures to ensure the safety of products produced by the company. Believer Meats has categorized such potential hazards into two general areas:

1. Potential hazards introduced into the food as a result of the production process (*e.g.*, culture media residues, microbial and environmental contaminants) which can be mitigated through appropriate controls; and
2. Hazards that are intrinsic to the identity and nature of the product (*i.e.*, genetic stability and nutritional composition) which can be evaluated through objective characterization of the product relative to an appropriate comparator with a long history of safe consumption (*i.e.*, chicken meat from a carcass).

Believer Meats has concluded that existing food safety assessment practices that have been applied to evaluate food ingredients and new food production technologies can be used for the safety evaluation of cultured animal cells. Accordingly, the general scientific procedures and safety evaluation practices described within this consultation dossier draw from the U.S. FDA's *Guidance for Industry and Other Stakeholders: Redbook 2000* (U.S. FDA, 2007), the U.S. FDA's 2016 *Final Rule on Substances Generally Recognized as Safe* (U.S. FDA, 2016), and the Agency's *Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives* (U.S. FDA, 2014). Believer Meats also notes that concepts discussed in the FDA's 1992 *Statement of Policy – Foods Derived from New Plant Varieties* offer useful parallels regarding the role of compositional testing and use of appropriate comparator foods for the hazard characterization of whole foods produced using novel technologies (FDA, 1992).

Believer Meats notes that the U.S. FDA has recently issued no objection letters pertaining to the safety of two cultured poultry meat products. These cell culture consultation evaluations were conducted on products defined as cultured *Gallus gallus* (chicken) myocytes (muscle) and fibroblast (connective tissue) cells grown as a cellular biomass or as intact "sheets of cells." Precedents from these consultations and corresponding information provided in the public facing narratives and FDA memo have therefore been considered during the preparation of this safety assessment (U.S. FDA, 2022b, 2023).

2.1 Safety Assessment Paradigm

For purposes of the discussion that follows, the term "cultured meat" means edible products derived from animal cells. Cultured meat products can be broadly defined as whole foods that display a defined yet broad compositional distribution of nutrients and cellular metabolites that contribute to the taste, aroma, and nutritive value of the food, and which are influenced by the species and tissue origin of the cells and the composition of culture media inputs used for growth and differentiation of the cellular biomass. Similar to the natural compositional variation of conventional chicken meat products harvested from various livestock sources, cultured meat products are inherently subject to compositional variance, and from a food safety evaluation perspective, the identity of cultured meat is operationally defined as a whole food rather than a defined chemical substance. It has long been recognized that whole foods consumed in large quantities in the diet do not lend themselves to the standard safety evaluation principles used for chemically defined ingredients/additives added to food, and that a quantitative assessment of the risk of individual whole foods from whatever source cannot be achieved (WHO, 1987).

Two historical precedents have influenced modern approaches to the safety evaluation of whole foods, namely foods processed using food irradiation technology and foods produced using plant genetic engineering methods. Although it can be hypothesized that cultured meat production technologies have the potential to produce unanticipated/unexpected compositional changes in the food that are of safety concern, these same concerns were raised during the evaluation of food irradiation and plant genetic engineering. For example, food irradiation was known to produce a range of unintended compositional effects *via* the production and reaction of radiolytic products and damage to micronutrients—effects that were verified through compositional testing. These concerns prompted a decade of research into the toxicity of food irradiation resulting in the sacrifice of tens of thousands of laboratory animals, including rats, mice, dogs, hamsters, quail, primates, and chickens. Findings from these studies did not yield any data that would call into question the adequacy of safety assessments that focused on compositional analyses of the food and comparisons with untreated food (Bartholomaeus *et al.*, 2013). Similar conclusions were reported by the World Health Organization (WHO).

> *[…] abundant and convincing data indicate that high-dose irradiated foods do not contain either measurable levels of induced radioactivity or significant levels of any radiolysis products distinct from those found in un-irradiated foods. The theoretical maximum levels that might be formed would be so low as to be of no toxicological consequence.* (Kaferstein, 1998)

The concept of using compositional similarity was born from lessons learned during safety evaluation of food irradiation where it became apparent that:

> *The application of "risk assessment" in the currently accepted sense is not appropriate to the toxicological assessment of foods preserved by high-dose irradiation. In this context, the concept of 'substantial equivalence' may be more appropriate*. (Kaferstein, 1998).

The safety evaluation of whole foods through compositional testing is based on the idea that the safety of any intended or unintended changes introduced to a food through the application of a novel processing technique can be assessed, in part, through a compositional comparison of the "new food" to its traditional counterparts that have a history of safe use in the food supply (FDA, 1992; FAO/WHO, 1996). A scientific procedures approach is applied to assess the safety of any changes that are identified under the intended uses of the "new food." It is recognized that compositional testing cannot comprehensively measure all the constituents of a food, which in some instances are likely to consist of thousands of molecules; therefore, the selection of an analytical plan is conducted on a case-by-case approach. Cases where an assessment of the novel processing technology identifies the potential for a new compound to be introduced to the food that does not have a history of safe use in the food supply may necessitate further safety evaluation using toxicological information characterizing the hazard of the newly introduced compound.

The use of compositional testing in the safety evaluation of a whole food requires identification of relevant "conventional comparator" product(s) with a history of safe consumption to which compositional comparisons can be established. In the case of cultured meat products, the conventional comparator could be sourced from edible tissue samples obtained from the same animal from which the cultured meat product is derived; however, it may be more robust to leverage available databases on compositional testing of conventional meat products to understand the natural variation of nutrients that are characteristic of the food. Compositional comparisons on other commonly consumed foods also may be relevant to the safety evaluation. A compositional testing approach requires an understanding of the potential hazards introduced during the production process (*e.g.*, media inputs) and from introduced genetic changes during cell line development to identify production inputs that may result in the introduction of a "new substance" to the meat product that is not normally present in the conventional comparator. Many of these concepts are discussed within the FDA's Statement of Policy-Foods Derived from New Plant Varieties (1992) and Consultation Procedures under FDA's 1992 Statement of Policy for Foods Derived from New Plant Varieties (FDA, 1992).

Compositional changes imparted by novel processing technologies can be characterized as intentional or unintentional. Unintentional changes are further divided into predictable *versus* unexpected changes (CODEX, 2008). Intended and predicted changes are readily evaluated by targeted testing approaches relative to appropriate comparators or published reference standards. In the case of cultured chicken products, predicted changes could include residues of the culture media present within the harvested biomass.

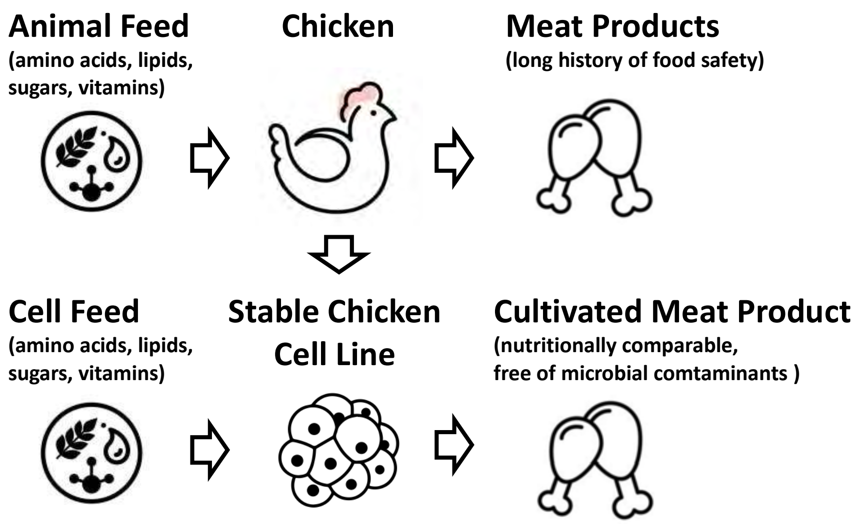
Unexpected effects of novel processing technologies on food composition are, by definition, more difficult to characterize. Notwithstanding obvious limitations in the ability to measure unexpected changes in a food, it is recognized that the biosynthetic outputs of an animal cell are defined by the unique gene expression patterns of the cell. Cellular outputs are therefore fixed to the inherent biosynthetic capacities of the cell unless heterologous genes are introduced into the genome through recombinant methods, which are not used by Believer Meats. Outside of the normal biosynthetic waste products of cellular activity (*e.g.*, lactic acid, ammonia), cells from common edible tissues (*e.g.*, muscle) are not known to produce toxic substances. Indiscriminate testing of the complete chemical composition of the cultured meat product is therefore not of practical value to a safety assessment.

Proteomics-based approaches could be used to characterize the protein composition at a qualitative level (*e.g.*, structural proteins, growth factors) relative to a comparator product; however, differences in protein composition are unlikely to be a safety concern as all ingested proteins are digested to the same amino acid components in a similar manner. It is therefore unlikely that further analysis of the protein identities of the meat cultures would be of nutritional or toxicological value.

Believer Meats has concluded that analytical testing should focus on characterizing the nutritional profile of the cultured meat product and include analyses for protein content, amino acid profile, fatty acid profile, minerals, and vitamins. Targeted testing for secondary metabolites, hormones, or growth factors originating from the growth media has been considered on a case-by-case basis. Analytical testing approaches also should consider potential contaminants that may originate from the environment or inputs and food contact surfaces that are used during the production process. Any change in the composition that is outside of the natural variation would then be evaluated for nutritional and toxicological impacts, if any. It should be noted that it is not necessary to demonstrate absolute compositional equivalence *per se*; it is about understanding the similarities and differences in composition so that expert judgement on the potential safety impacts, if any, can be understood.

Similar views have been expressed by the FDA within the agency's guidance documentation on new plant varieties where such techniques were recognized to potentially alter the composition of the food in a manner that was relevant to food safety; however, the agency concluded that the likelihood of a safety hazard from such genetic changes would be typically very low in situations where a food product had a very long-history of safe food consumption, particularly for situations where the 'modified' organism was not known to exhibit metabolic capacities for the production of undesirable substances (FDA, 1992). Believer Meats' cultured chicken fibroblasts have not been genetically modified using recombinant methods, therefore, the cellular composition of cultured chicken fibroblasts is regulated by similar genetic controls and biosynthetic pathways that function within fibroblast cells within live animals (see Figure 2.1-1). Accordingly, the composition of cultured chicken is expected to fall within the natural range of conventional chicken products. All of the culture media nutrients are similar to vitamins, minerals, natural metabolites, hormones, and growth factors that either are consumed as animal feed or are synthesized within the animal and that are necessary to sustain the growth and development of tissues. No DNA sequences encoding for toxic or other undesirable substances are known to exist in chicken cells; therefore, outside of well characterized waste products of nitrogen and carbon metabolism (*e.g.*, ammonia, lactic acid), cultured chicken cells will not possess biosynthetic mechanisms for the synthesis of unexpected or undesirable substances. When considering the long history of safe consumption of conventional chicken, the safety of cultured chicken can be evaluated through the use of a compositional testing strategy that considers common and essential nutrients present in suitable comparators derived from conventional chicken, potential transfer of residual media components from the culture process into the finished product, and other hazards that may be introduced during the production process (*e.g.*, food contact material, environmental, and microbial contaminants).

Figure 2.1-1 Safety Evaluation of Cultured Chicken Fibroblasts



<u>Note:</u>
- Chicken DNA does not encode any known toxins or novel unexpected compounds.
- Chicken cell lines produced without DNA recombination, use the same genetic and nutrient converting pathways encoded in the bird.
- Safety is therefore based on verification of genetic stability and compositional testing.

Data and information presented within this consultation notice describe the identity of Believer Meats' cultured chicken fibroblasts. Believer Meats has produced a cultured fibroblast cell line from the fertilized egg of an Israeli Baladi chicken. A description of the production process, starting from procurement of the primary cells to development of the cell lines, creation of master cell banks (MCBs) and manufacturer's working cell banks (MWCBs), scale-up and production of the cells in a bioreactor, and harvesting of the finished products, has been published in detail in a peer-reviewed journal of the Nature Publishing Group (Pasitka *et al*., 2023) and is summarized herein as it applies to the company's commercial process. Believer Meats' Food Safety Plan, which includes a comprehensive evaluation of potential hazards throughout the production process and, where appropriate, controls for mitigating risk, is summarized herein. The safety of Believer Meats' cultured meat products was evaluated using compositional comparisons to conventional chicken tissues and other commonly consumed whole food products combined with targeted analyses for other hazards that may be introduced to the product as a result of the novel production process (*e.g.*, environmental hazards, media residues).

3.0 PRODUCT IDENTITY AND INTENDED USE

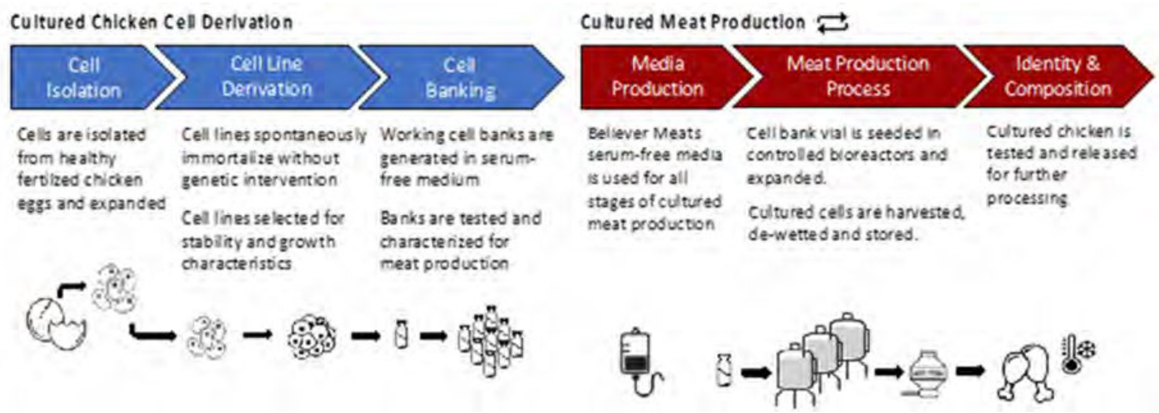
3.1 Chicken Meat

For the purposes of this discussion, the term "meat" is used in its ordinary sense to mean the flesh of animals used as food. The composition of conventional "chicken meat" is generally influenced by the genetic background of the animal, rearing environments, dietary factors, and anatomical location of the tissue within the animal from which the meat is produced. The identity and quality characteristics of chicken meat can be defined by its nutritive value and sensory characteristics and the absence of relevant environmental contaminants that may be of human safety concern (*e.g.*, heavy metals, microbial contaminants). Due to the long history of safe consumption, meat safety has historically been evaluated exclusively by the degree of potential microbiological and chemical contamination (*i.e.*, there are no intrinsic hazards in chicken meat). The nutritional quality of conventional chicken meat depends on the content of high-value protein, fatty acids, vitamins, macro- and micronutrients, and other nutritive compounds. Further, meat color, aroma, and flavor are essential sensory traits (Sokołowicz *et al.*, 2016). At a microscopic level, chicken meat is a tissue product comprised of mesenchymal lineage cells (*i.e.*, fibroblasts, myocytes, and adipocytes), each with different cellular functions that together contribute to the texture, nutritional value, and flavor of the meat. The cellular composition, growth, and differentiation of eukaryotic cells within an animal are controlled by the cellular DNA and influenced to a large extent by the extracellular milieu of essential and non-essential nutrients originating from the animal's diet and by a mixture of endocrine and paracrine signals within the animal.

3.2 Cultured Chicken Fibroblast Cells

The process of producing cultured chicken using cells isolated from a bird requires bioprocessing techniques that recapitulate many of the growth and differentiation processes necessary to sustain the growth and viability of cells within a live animal as discussed in Section 3.1 above. Accordingly, Believer Meats' process provides nutrient-rich environments for cell growth, bioactive components for maintenance of cell proliferation and differentiation, and active processes for maintenance of the cellular environment related to pH, gas exchange, and removal of waste products in a manner that is biochemically similar to processes that occur within the animal. As cell identity is intrinsically linked to its genetic composition and extracellular environment, cultured meat cells will be similar to cells present within meat tissues. The identity of a cultured chicken cell is therefore be defined through verification of the species identity (*i.e.*, *Gallus gallus*), and secondary measures also can be obtained to characterize cellular markers linking the cells to a mesenchymal lineage (*e.g.*, muscle, fibroblast, adipocyte), and compositional analyses that focus on the nutritional elements of the biomass.

Figure 3.2-1 Overview of Cultured Chicken Production Process



Believer Meats' proprietary process derives cultured chicken cell lines from fertilized eggs of *Gallus gallus domesticus* (domestic chicken). Briefly, chicken fibroblasts are isolated and expanded until small populations of cells spontaneously break through the replicative limits, producing continuously expanding lines of chicken fibroblasts characterized by stable population doubling (PD) times. The cell lines are adapted to growth in suspension, which is necessary for volumetric scale-up of the cells. The cell lines are finally adapted to grow in serum-free media and stored in cell banks that are tested and characterized.

Believer Meats produces cultured chicken products by seeding banked cells into bioreactor tanks and expanding the cells until a sufficient volume of cultured chicken mass is produced. The cells are then separated from the media using filtration methods and washed to produce a cellular biomass of cultured fibroblasts that are 'harvested' from the bioreactor and further processed into finished products using conventional food processing techniques. Believer Meats' cultured fibroblast products that are the subject of this consultation are depicted below in Figure 3.2-2 and are produced from the company's fibroblast cell lines. The cell lines and manufactured biomass produced from these cell-lines are the subjects of this consultation are generically referred to as 'chicken cells' and 'cultured chicken cells' as well. A description of the sourcing and production of these cell lines is described in greater detail in Section 4.0.

Believer Meats' cultured chicken cell products can be mixed with plant-based ingredients and other permitted food ingredients and processing-aids and extruded into finished food products (*e.g.*, chicken breast). Cultured chicken products produced by Believer Meats will therefore be fully substitutional to current food products that can be produced using chicken meat from an animal carcass.

Figure 3.2-2 Pictorial Examples of Finished Food Products Produced Using Believer Meats Cultured Chicken Fibroblast Cells (Uncooked Cultured Chicken Pieces, Grilled Cultured Chicken Breast)

Cultured Chicken (uncooked and sliced)	**Cultured Chicken Breast** (grilled)