CAPI
THE CANADIAN AGRI-FOOD POLICY INSTITUTE

"Friend" or "Fiend":

In vitro lab meat and how Canada might regulate its production and sale

Paper prepared for CAPI

by

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Abstract

In vitro meat is an emergent technology gaining significant public interest. As technology races forward, it is imperative that regulations keep up. Innovation in the food sector is increasingly important and having regulations that effectively protect consumers while providing industry oversight of this new technology is necessary. Presently, *in vitro* meat does not have a regulatory framework that governs its production and commercialization. This paper explores the science behind producing *in vitro* meat and the possibility of adapting the current Guidelines for Safety Assessment of Novel Foods ("Guidelines") in Canada to regulate *in vitro* meat.

These Guidelines are accommodative for a plethora of novel technologies for foods derived from plants and microorganisms and possibly could provide a flexible framework to regulate *in vitro* meat. The findings in this review suggest that the current regulations for novel foods serve as a good platform to build a framework to regulate *in vitro* meat. Looking ahead, the regulations would need to be developed further to ensure a high level of scrutiny for *in vitro* meat production and commercialization.

1. Introduction

1.1 Cellular agriculture

> *Imagine train car after train car, all en route to a medical factory, filled with nothing but pig and cattle pancreases. As tough as it is to imagine today, nearly four decades ago, that's how we made insulin for diabetics. At the time, it took some 23,500 farm animal pancreases simply to produce a single pound of insulin, meaning that pharma giant Eli Lilly purchased the pancreases of 53 million animals each year. Thankfully, diabetics no longer need to inject themselves with parts of pig pancreases.*
>
> *Instead, they have access to a safer and more reliable therapy: actual human insulin. No, they're not relying on cadavers. Instead, they can thank the scientists at a then-start-up called Genetech, which figured out how to engineer bacteria to make human insulin.*
>
> *Today, a group of promising start-ups is further refining this process and taking it out of the medical space, using it to produce everything from egg whites and milk to leather and gelatin, all without the animals*[1] (Shapiro, 2018).

This field is called cellular agriculture and it is defined as the production of agricultural products from cell cultures. This paper will specifically focus on one product of the field of cellular agriculture: *In vitro* meat.

2. What is *in vitro* meat?

In vitro meat (sometimes referred to as cultured meat, clean meat or synthetic meat) involves fabricating meat for human consumption wherein the protein cells obtained from an animal's muscle tissue are synthesised in a lab (Sharma, Thind & Kaur, 2015). The methodology was inspired by regenerative medicine for reconstructing deteriorated muscle tissue of patients from their own cells.

Briefly speaking, *in vitro* meat is obtained when a few stem cells are harvested from an unharmed living animal and then cultured in a growth media which allows for cell division and cell proliferation. The cells are precursors to the specific kinds of tissue they are capable of forming through cellular mass growth in the growth media. The cells differentiate into muscle cells which then fuse to form muscle fibres (Post, 2012). Dr. Schulze, Vice President of product and regulation at Memphis Meats, a start up in Silicon Valley working on cultured meat research, stated in an interview that it is possible to produce up to 10,000 cows' worth of meat with a single biopsy of animal cells (Food Navigator, 2018).

[1] Italicized content in this paper indicates direct quotations from the referenced sources.

3. Why develop *in vitro* meat?

The provision of universally accessible, affordable, safe and sustainable protein is in line with the United Nations Sustainable Development Goals ("21st-century protein") and is a pressing issue that cuts across systemic challenges, such as consumption, the environment, food security, health and trade issues (World Economic Forum, 2018). Several arguments are raised for the early adoption and production of *in vitro* meats. Five such arguments are reviewed below: Food Security, Food Efficiency, Sustainability, Animal Welfare and Human Health.

3.1 Food Security

In vitro meat can contribute to improving nutrition and access to meat around the world. Due to the increasing world population in developing economies and subsequent rise in meat consumption as illustrated in Figure 1, it is predicted that meat consumption will double in the coming forty years (FAO, 2012). In 1960, 45 million tonnes of meat (beef, pork and chicken) was globally consumed. Within a span of one generation, due to factors like urbanization, rise of the middle class and increasing affluence, the demand for meat has risen dramatically. In 2018, meat production globally stands at 263 million tonnes and is expected to nearly double to 445 million tonnes by 2050.

For many people, animal proteins are an important source of nutrients (i.e. iron, minerals etc.). However, benefits of this expansion in global meat consumption have not been universally distributed. 815 million people around the world are still malnourished and although today's global average meat consumption is 100g per day, consumption per capita in some countries is significantly less. Ensuring that more people around the world have access to this excellent source of nutrients, could help achieve one of the most important Sustainable Development Goals of the United Nations (ie malnutrition) (World Economic Forum, 2018).

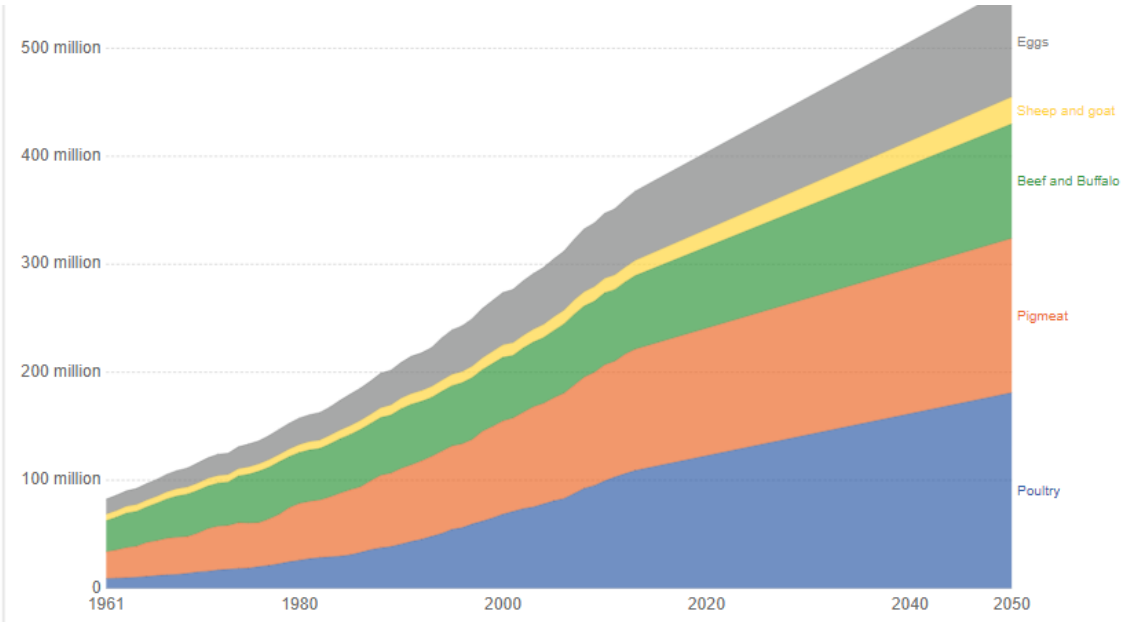

Figure 1: Global meat consumption projections to 2050[2] Source: (Alexandratos and Bruinsma, 2012).

3.2 Food Efficiency

In vitro meat offers society a very efficient way to manufacture and consume animal protein. Scientists argue that cows and pigs have a low bioconversion rate. For every 100g of vegetable protein that is fed to them, they produce 15g of animal protein; thereby they have a bioconversion rate of 15% (Egbert & Borders, 2006; Pimentel & Pimentel, 2003), which is quite low. Producing a high amount of protein with fewer resources as input is one of the challenges that *in vitro* meat production aims to address. Bhat et al. argue that *in vitro* meat production would take less time before harvesting with fewer energy and labour requirements (Bhat et al., 2015).

3.3 Sustainability

A report released by the Food and Agricultural Organisation (FAO) in 2006 found that meat production contributes more greenhouse gas emissions (GHG) such as carbon dioxide, methane and nitrous oxide than transportation or industrial sectors (Steinfeld et al., 2006). According to Datar and Betti, it is estimated that world meat production contributes between 15 and 24% of global anthropogenic GHG emissions with a significant share due to deforestation that often takes place in order to create new pasture land for livestock, such as in the Amazon (Datar and Betti 2010, Steinfeld et al., 2006). Tuomisto and de Mattos suggested that *in vitro* meat production could lead to a large reduction in GHG emissions (Tuomisto & Teixeira de Mattos, 2011). It is argued that natural resources could be spared from depletion if *in vitro* meat made a significant contribution to the world meat supply, since it is produced using a vertical production method which requires less space, and would avoid requiring large amounts of deforestation, such as of the Amazon rainforest to make way

[2] Eggs are present in this graph because it is a source of animal protein but it will not be relevant in this review.

for cattle grazing (Rother, 2003). Such savings also lead to reduced threats to biodiversity and more carbon dioxide absorption by rainforests (Kadim et al., 2015).

This potential has been assessed in Life Cycle Assessments, based upon hypothetical models of what production methodology *in vitro* meat production would take. Stephens et al., (2018) summarise the hypothetical models as follows:

Tuomisto et al., 2011	In comparison with conventionally produced beef, pork, sheep and chicken, *in vitro* meat could lead to 78-96% less GHG emissions, 99% less land use, 82-96% less water use and 7-45% less energy use depending on the meat, although poultry uses less energy.
Mattick et al., 2015	The model used in this study has notable differences in media production technique and inclusion of a cleaning phase. It suggested that *in vitro* meat could involve significant energy use leading to cultured meat having greater global warming potential than pork or poultry, but lower than beef while maintaining the same reduction in land use.
Smetana et al., 2015	A cradle to plate assessment was conducted to compare *in vitro* meat to a range of alternatives such as plant-based, mycoprotein-based, dairy-based meat and chicken. They found that *in vitro* meat had the highest impact due to highest energy level requirements, with significant reductions in freshwater ecotoxicity and land use.

All three Life Cycle Assessments note that *in vitro* meat has significant scope for innovation that could reduce energy consumption hypothesised in the assessments, thereby delivering better environmental outcomes than the models (Stephens et al., 2018). The large reduction in land use for agriculture may also lead to restoration of wildlife habitat and utilisation of the land for other purposes (Bhat et al., 2015).

3.4 Animal Welfare

Canadian federal law contains several provisions to promote and protect animal welfare. Under the *Health of Animals Act*, for example, farmed animals must be treated in an appropriate way when they are loaded onto transport trucks and at slaughter plants. Despite these provisions, there are still concerns over the way animals are being treated. Consumers globally have a growing interest in food ethics and the way animals are raised and bred (Williamson 2003).

With the increase in meat consumption worldwide, there is concern that more intensive animal production is leading to animal welfare issues and poor treatment of animals. Animal welfare has become a serious concern for consumers as a result (Sharma, Thind & Kaur, 2015).

3.5 Human Health

Salmonella, *Campylobacter* and *Escherichia coli*, which are pathogens found in meat, cause millions of episodes of illnesses each year (CDC, 2012). In 2017, the Public Health Agency of Canada (PHAC) in collaboration with the Canadian Food Inspection Agency (CFIA) and Health Canada (HC) investigated an outbreak of *Salmonella enteritidis* infection which spread to 5 provinces in Canada caused due to frozen raw breaded chicken products (PHAC, 2017).

In vitro meat can help combat such outbreaks since the conditions in which cell culturing is carried out is sterile, potentially mitigating the spread of diseases originating in animals (Kadim et al., 2015). Additionally, it is also possible to eliminate food exposure to products which are hazardous to consumers such as pesticides, fungicides, heavy metals and antibiotics (Marques et al., 2011).

Since animals will not have to be bred in large numbers, the spread of zoonotic diseases caused by close confinement of animals will also be reduced (Datar and Betti., 2010). In 2017, the US Food and Drug Administration banned the use of antibiotics solely to induce animal growth. Despite the restrictions, nearly 80% of US antibiotics sales still go towards livestock. This fact raises public health concerns about increased antibiotic resistance which leads to nearly 23,000 deaths in America each year, according to the the Centers for Disease Control and Prevention (CDC) (Aleph Farms Ltd, 2018).

4. How will *in vitro* meat potentially be manufactured: A few more details?

4.1 Introduction

The inception of the idea to create meat through non-conventional means can be traced back nearly 80 years ago when Frederick Edwin Smith predicted that it would be unnecessary to go to the extravagant length of raising and rearing a bullock in order to eat steak (Smith, 1930). Shortly afterwards, Winston Churchill said that we would soon escape the absurdity of growing a whole chicken in order to eat separate parts of it (Churchill, 1932).

Today, science has made *in vitro* meat a reality. There are two broad classifications of the methodologies that can be employed, namely, *self-organising technique* and *scaffold-based technique.*

The *self-organizing technique* involves using a biopsy or explant from the donor animal, which is proliferated in a nutrient medium under ambient conditions. This technique can be applied for producing *in vitro* meat since the tissue formed would closely resemble conventional meat in its composition, containing muscle cells, fat and other cells in familiar proportions (Sharma, Thind & Kaur, 2015). The meat produced will have a well-defined three dimensional structure which increases the organoleptic characteristics of meat (Edelman 2003). Proliferation of cells in the culture media and the requirement to collect multiple biopsies from donor animals are some of the challenges in this technique (Sharma, Thind & Kaur, 2015).

Scaffold-based technique is embryonic myoblasts or adult skeletal muscle cells which are proliferated and then attached to a scaffold which is perfused in a culture medium. This method results in the formation of myofibres which may then be harvested, processed and consumed as meat products (Bhat & Bhat, 2011).

An illustration of the manufacturing process of an *in vitro* meat production system (IMPS) using the *self-organizing technique* is depicted in Figure 2, and an IMPS using scaffold-based technique is shown in Figure 3:

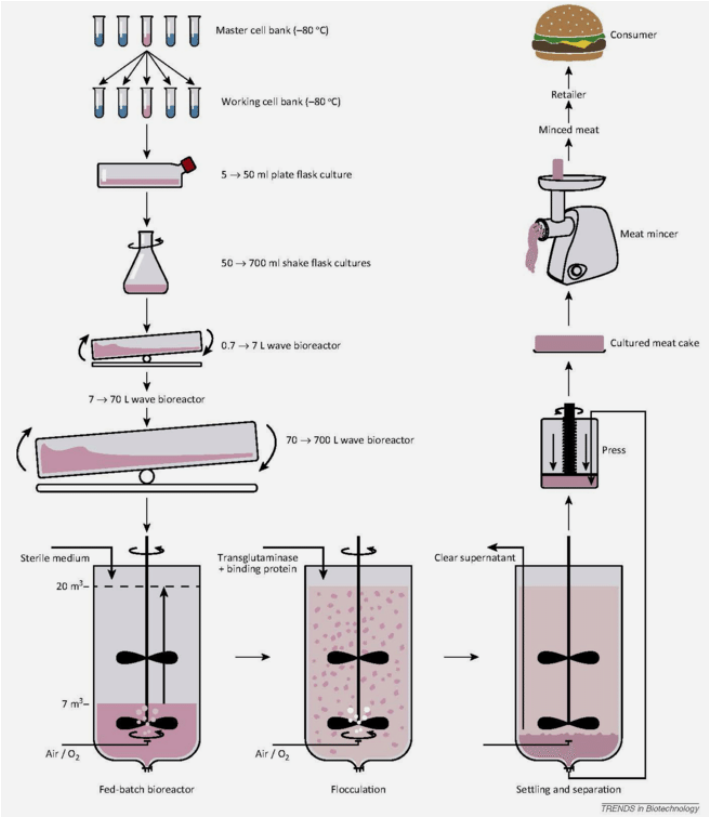

Figure 2: Manufacturing process (self-organizing technique), Source: van der Weele & Tramper, 2014

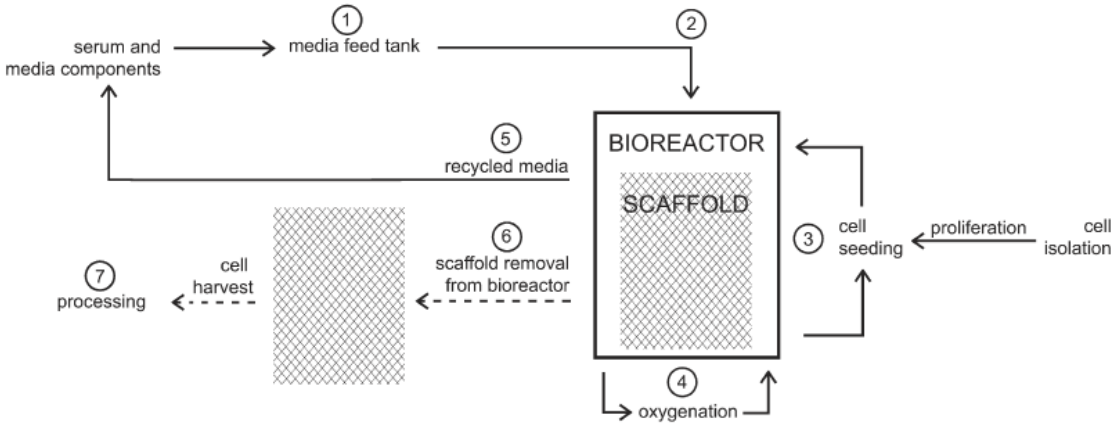

Figure 3: Manufacturing process (Scaffold-based technique), Source: Datar and Betti, 2010.

The components of IMPS are stated below:

4.2 Cells

Different cell varieties have been proposed by various authors such as myosatellite stem cells[3], embryonic stem cells[4] and adult stem cells[5] .There is also the possibility that the cells used may be genetically modified. One of the main reasons why genetic modification may be required is to ensure that cells have the ability to proliferate for a long period of time, thereby producing a large quantity of cultured meat.

Cells will have to be genetically modified due to their limited proliferation capacity and their ability to develop mutations over time. In a cell culture, cells are believed to undergo a fixed number of doublings called the Hayflick limit. The Hayflick limit for farm animals has not been established, however, satellite cells cloned from a turkey breast muscle express telomerase. Telomeres are repetitive nucleotide sequences at the end of a chromosome, which protects the chromosome from deterioration and fusion with neighbouring chromosomes in the cell. Telomere length shortens as an individual cell age's. Progressive shortening of telomeres leads to apoptosis (programmed cell death) of somatic cells (Shammas, 2011). Some species may generate enough daughter cells, which in turn generate huge quantities of cultured meat. For other species, it may be necessary to transfect a telomerase gene with a higher Hayflick limit in order to ensure that a high proliferation rate is present (Edelman et al., 2005).

4.3 Culture Media

Myoblast (muscle cells which have the potential to develop into a muscle fibre) culturing usually takes place in animal sera which is expensive and incapable of lending itself to large scale cell culturing. Animal sera are derived from an adult, newborn or fetal source and fetal bovine serum is the standard for cell culture media (Coecke et al., 2005). Media which are animal-serum free reduce both operating costs as well as lessen potential pathogens (Froud, 1999). McFarland et al. developed a serum-free medium that supported the proliferation of turkey satellite cells in culture (McFarland, 1999). Shortly after this, a serum comprised of maitake mushroom was created which was both serum free and capable of achieving higher rates of growth of cells in comparison to fetal bovine serum (Benjaminson et al., 2002).

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[3] This is the preferred cell type currently suggested for an IMPS due to its high efficacy with the myogenesis process. However, they are a rare muscle tissue with a limited ability to self-renew (Post 2012; Bhat 2011).

[4] An attractive option for IMPS is to have cells with an unlimited self-renewal capacity in order to avoid taking multiple biopsies from the donor animal. However, genetic mutations occur in the cell lines over time thereby limiting production potential (Mattick and Allenby 2010; Datar and Betti., 2010).

[5] Adult Stem Cells differentiate only into a certain type of cell therefore the preferred cell type for IMPS is epithelial stem cell since it forms muscle tissue, which is the primary component of meat (Williams 2012). The biggest shortcoming of using adult stem cells is that they are prone to malignant transformation. These cancerous cells are probably harmless since they are digested in the human stomach and intestine so it is unlikely that they will be incorporated into the live body but this is a sensitive consumer question and should be studied to ensure official authorisations are obtained before bringing the product into the market (Hocquette, 2016).

Culturing of cells can be divided into two phases: the proliferation phase and the differentiation phase. The goal of the proliferation phase is to obtain the maximum number of cells from the biopsy and then differentiate them into skeletal muscle cells and coerce them with specific conditions to produce maximum protein. This occurs naturally with myosatellite stem cells which are then cast in a collagen-like gel or temporary biodegradable scaffold (Post, 2012). However, this is an area of research that is yet to produce a comparable and affordable alternative to animal sera (Butler, 2015).

4.4 Scaffold

Typically, a scaffold should have a large surface area in order to enable attachment and growth of cells and have properties which enable it to be flexible to allow for contraction and must easily disassociate from the final product of meat which is produced (Datar and Betti., 2010). Scaffolds must closely mimic the *in vivo* condition in order to enable myotubes to differentiate optimally with a stiffness and structure which is similar to a tissue derived from conventional meat (Engler et al., 2004). The drawback with scaffold-based techniques are that they cannot produce highly structured meats like steaks but only produce boneless meats with a soft consistency (Bhat et al., 2015). Different types of edible and inedible polymers such as cellulose and collagen which are permitted food additives have been suggested as the base material for scaffold development which would lead to the aforementioned desired properties (Williams 2012).

4.5 Bioreactor

In order to promote ambient conditions for the muscle tissue to grow, it is necessary to have a sterile condition in a favourable environment with adequate levels of culture medium perfusion (passage of culture medium through the system) (Datar and Betti., 2010). The basic objective of employing a bioreactor in IMPS is culture medium perfusion. For large-scale commercial production of *in vitro* meat, bioreactor stands as a giant requirement of IMPS because the cells need a closed and large surface area for culturing, proliferation and differentiation in sufficient numbers (Bhat and Bhat 2011; Martin et al. 2004). The key contributions of a bioreactor to an IMPS are that tissue assemblies can be easily suspended, fluid shear is low and cells are in near-continuous suspension. As far as theoretically scaling-up lab-type designed bioreactors, scaling-up to industrial scale should not affect the physics of the method of functioning (Edelman et al. 2005).

4.6 Fields

Provision of mechanical, electromagnetic, gravitational and fluid flow fields affect the proliferation and differentiation potential of myoblasts (Kosnick et al., 2003). Powell and others found that repetitive stretch and relaxation equal to 10% of length, six times per hour, increased differentiation of cells into myotubes (Powell et al., 2002). Yuge and Kataoka seeded myoblasts with magnetic microparticles and induced cell differentiation by placing them in an electric field which did not require growth factors. However, this may impinge on regulatory acceptance since acceptance of magnetic microparticles as a food additive might be problematic (Yuge and Katoka, 2002). Electrical stimulation also contributes to differentiation and sarcomere formation within

established myotubes (Kosnick, 2003).

4.7 Oxygen Carrier

Cell density and viability correlate positively with the oxygen gradient in tissue cultures which are grown statically (Radisic et al., 2008). Similar to what blood provides in an *in vivo* environment, oxygen carriers can be supplemented to the culture medium to maintain high oxygen concentrations in a solution. Oxygen carriers may either be modified versions of haemoglobin or artificially-produced perfluorochemicals (PFCs) since they dissolve large volumes of oxygen and therefore can perform the same function as hemoglobin (Lowe, 2006). Development of an artificial blood is an active area of research and many applicable options are likely to arise with time (Datar and Betti., 2010).

5. Challenges that the new technology could face.

5.1 Mimicking *in vivo* conditions

The main obstacle of producing cultured meat is to mimic the *in vivo* conditions of the animal. The evolution of the mechanism of muscle development has occurred over millions of years and is an efficient process that is best suited to occur inside the animal body as part of a host of other functions. Up until now, tissue engineering has focused on medical applications such as regenerative medicine or models used in drug discovery and toxicology studies. While the underlying principle may be the same, the scale at which meat must be produced is enormous and it must be an affordable commodity. However, since cultured meat is a food product and not a medical product, the regulatory requirements can afford to be less stringent (Stephens et al., 2018).

As discussed previously, tissue engineering for *in vitro* meat relies on myosatellite stem cells as this differentiates to form muscle tissue which is the major constituent of meat. Replicating the biology of a muscle is the main goal which requires a complex system containing multiple cell types and a replicated blood vessel network to provide desirable taste. A goal which can be targeted for the near future is producing a muscle protein ingredient based on muscle cells alone (Stephens et al., 2018). This is because a majority of skeletal muscle analysis has been carried out in 2D experiments using cell lines (Burattini, 2004). 3D structures are being investigated as an alternate *in vitro* model since it represents conventional skeletal muscle tissue (Snyman, Goetsch, Myburgh, & Niesler, 2013).

5.2 Possibility of adding antibiotics which may decrease marketability

Culture media used in IMPS for both stages of skeletal muscle development are supplemented with 10% to 20% growth media (Hinds, Bian, Dennis, & Bursac, 2011, Mudera et al., 2010) and 0.5-2% of horse serum or foetal calf serum is added at the differentiation stage (Chiron et al., 2012). Chicken embryo extract is also added to some cultures. In addition, it is common practice to add an antibiotic or antimitotics in cell cultures to prevent infection of long-term cultures. In order to utilise

commercial media in a product, a Life Cycle Assessment must be carried out to ensure that it is safe to use. However, in most cases, due to the proprietary nature of commercial media, obtaining this information may be problematic (Stephens et al., 2018). Furthermore, adding antibiotics and antimitotics may result in decreased consumer acceptance.

5.3 Developing scaffolds

In order to imitate the growth environment that is present inside the animal, a scaffold is required which showcases characteristics that are favourable for cell adhesion, cell proliferation and tissue development. Scaffolds used in muscle tissue engineering have been extensively described in the literature (Chan & Leong, 2008; Sakar et al., 2012). Successful scaffolds for 3D muscular development and formation *in vitro* are all animal-derived due to factors like fiber alignment, comparability to an *in vivo* system and cell adhesion properties (Bian et al., 2009). There is a further consideration about scaffolds: should the scaffold be a part of the product thereby being edible and degrade after the cell culturing process is complete or should the scaffold be removed from the adherent cells and be reused?

Cost is an importance factor and it is expected that novel scaffolds will be developed as cultured meat products themselves are being developed (Stephens et al., 2018). Other considerations which should be taken into account for scaffold synthesis include the use of medical grade collagen, fibrin, thrombin or animal derived products like hydrogels to mock the *in vivo* niche of the animal (Chen, Nakamoto, Kawazoe, & Chen, 2015).

5.4 "Franken-food"

Perceived naturalness of foods for consumer appeal is also an important factor that must be taken into consideration. Existing studies on perceptions towards *in vitro* meat show that consumer opinions range from very supportive to very negative, with many shades of uncertainty in between (Stephens et al., 2018). Studies of social media comments indicate that the unnaturalness of meat can be a problem (Laestadius & Caldwell, 2015), noting that these platforms can be a key site of resistance (O'Riordan et al., 2015). An online survey of 673 participants based in the United States reported that while over two-thirds of respondents said they would try *in vitro* meat, only one-third would regularly eat it (Wilks & Phillips, 2017). Lincicum argues in his paper that the inhibition towards trying novel foods is derived from "naturalistic fallacy" which is the tendency to erroneously equate the natural to the good. Numerous naturally-derived foods are pernicious for human health, and yet no one would suggest not consuming them. Furthermore, Lincicum (2010) argues that important life-saving advances in medicine are profoundly unnatural, yet are rightly applauded (Lincicum, 2010). Stephens et al. state that should *in vitro* meat enter the market, it is probably going to be after other cellular agricultural products such as egg white and milk have been introduced and accepted by consumers. This may subsequently help sway the public perception of *in vitro* meat (Stephens et al., 2018).

Micheal Selden, the co-founder of the company Finless Foods which grows lab-grown fish stated (Poinsky, 2018):

> *We are not a scooter rental company; we cannot just throw our food on the market and assume that people will trust us. Food is considerably more personal than that. We need to first show people what we are working on and how safe it is in order to gain their trust due to evidence, and get them to believe in what we are making as much as we do.*

5.5 Cost

A lab-grown meat burger has fallen from $325,000 in 2013 to $11.36 in 2018 (CNN, 2018). Memphis Meats is working to produce *in vitro* chicken meat which would currently retail at $6000 per pound, whereas Beyond Meat's plant-based burgers cost merely $12 per pound. However, all of these are far more expensive than conventional beef which costs consumers nearly $4 per pound, on average, according to the USDA (Purdy, 2017).

Tyson Foods, Cargill Inc, Bill Gates and Richard Branson have recognised the market potential of cellular agriculture and have invested in companies like Memphis Meats and Future Meat technology (Edney, 2018). At the Reducetarian Summit in New York, David Kay of Memphis Meats said that they target to price their products at a premium and bring it to markets by 2021 (Cosgrove, 2018).

5.6 Discrepancy over the definition

On June 19th, 2018, CBC reported that there is a war of words over what to call lab-grown meat. Animal rights advocates are pitted against cattle ranchers with regulators yet to decide the terminology. 'Clean meat' is advocated by the supporters of the technology due to research indicating that lab-grown meat will be safer to consume and is produced in a sterile manner. However, Danielle Beck, director of government affairs for the National Cattlemen's Beef Association says that this would imply that traditional beef is dirty (CBC News, 2018).

On February 9th 2018, the US Cattlemen's Association (USCA) filed a petition with the US Department of Agriculture (USDA) seeking to allow only meat derived from animals grown and slaughtered traditionally to be labeled as beef or meat. That would disallow companies like Impossible Foods Inc. which makes plant-based mock meat, as well as meat potentially grown in a lab, to label their products as meat (USCA petition, 2018). Officials from the Food and Drug Administration (FDA) planned to hold a meeting on July 12th 2018 to make that determination (Edney, 2018). A start-up in Israel called Aleph Farms argues that *in vitro* meat is antibiotic-free and grown in a controlled and sterile environment with advanced 3D cellular agricultural technology, thereby seeking to label the new technology as 'clean meat'. However, USCA may perceive this labeling as a threat to their business implying that conventional meat is unclean. (Fortune, 2018).

According to Labelling Requirements for Meat and Poultry Products of the Canadian Food Inspection Agency (CFIA) –

> *Meat and poultry products include all products that contain more than 2% poultry or meat. Examples of meat include beef, veal and bison, whereas examples of poultry include chicken and turkey* (CFIA, 2018).

As proposed, *in vitro* meat would possess far less than 2% of *original* animal cells (Lincicum, 2010). Therefore, it is important for regulators to address if the proliferated cells qualify as "meat" and come under the definition of meat which is stated as per CFIA requirements.

6. Would *in vitro* meat be regulated as a novel food in Canada?

In vitro meat will likely be held to be a novel food in Canada because (1) it does not meet the current definition of meat in Canadian law; (2) certain components that go into making the *in vitro* meat are novel; and (3) it may be genetically engineered.

According to Division 28 of Part B of the Food and Drug Regulations, a "novel food" means:

> *a)a substance, including a microorganism, that does not have a history of safe use as a food;*
>
> *b)a food that has been manufactured, prepared, preserved or packaged by a process that*
>
> *i.has not been previously applied to that food, and*
> *ii.causes the food to undergo a major change; and*
>
> *c)a food that is derived from a plant, animal or microorganism that has been genetically modified such that*
>
> *i.the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,*
> *ii.the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or*
> *iii.One or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for the plant, animal or microorganism.* (Food and Drugs Regulations CRC, c 870: Novel Foods)

The process of using IMPS (*in vitro* meat production system) is something that has never been applied to produce meat. Conventional meat is derived from animal carcasses. According to the Canadian Food Inspection Agency (CFIA), meat is defined as:

> *The edible part of a carcass that is the muscle associated with the skeleton, tongue, diaphragm, heart, gizzard or mammalian oesophagus, with or without accompanying and overlying fat, together with those parts of the bones, skin, sinews, nerves, blood vessels and other tissues that normally accompany the muscle and are not ordinarily removed in dressing a carcass, but does not include the muscle associated with the lips, snout, scalp or ears, mechanically separated meat or meat to which an ingredient other than meat has been added* (CFIA, 2018).

As discussed previously, the process of producing *in vitro* meat is independent of the animal and is synthesised in a lab using a bioreactor. Therefore, this qualifies as a food that has been manufactured, prepared, preserved or packaged by a process that has not been previously applied to that food. Certain components which go into synthesising the meat such as the culture media, scaffolds and artificial blood which act as oxygen carriers have never been previously designed for human consumption.

In vitro meat cell lines may potentially be produced using genetic engineering techniques since several laboratories are pursuing this route (Stephens et al., 2018). Therefore, there is a possibility that it may be a food which is derived from genetic modification.

What is interesting to note here, which is unique to *in vitro* meat, is that despite potentially being a product of genetic modification:

i. The characteristics that it displays are similar to the animal it is obtained from;

ii. The donor animal is in no way affected by the genetic modification since it occurs in the cells, independent of the animal it is derived from; and

iii. The characteristics displayed by the meat produced falls within the anticipated range of the animal it is derived from.

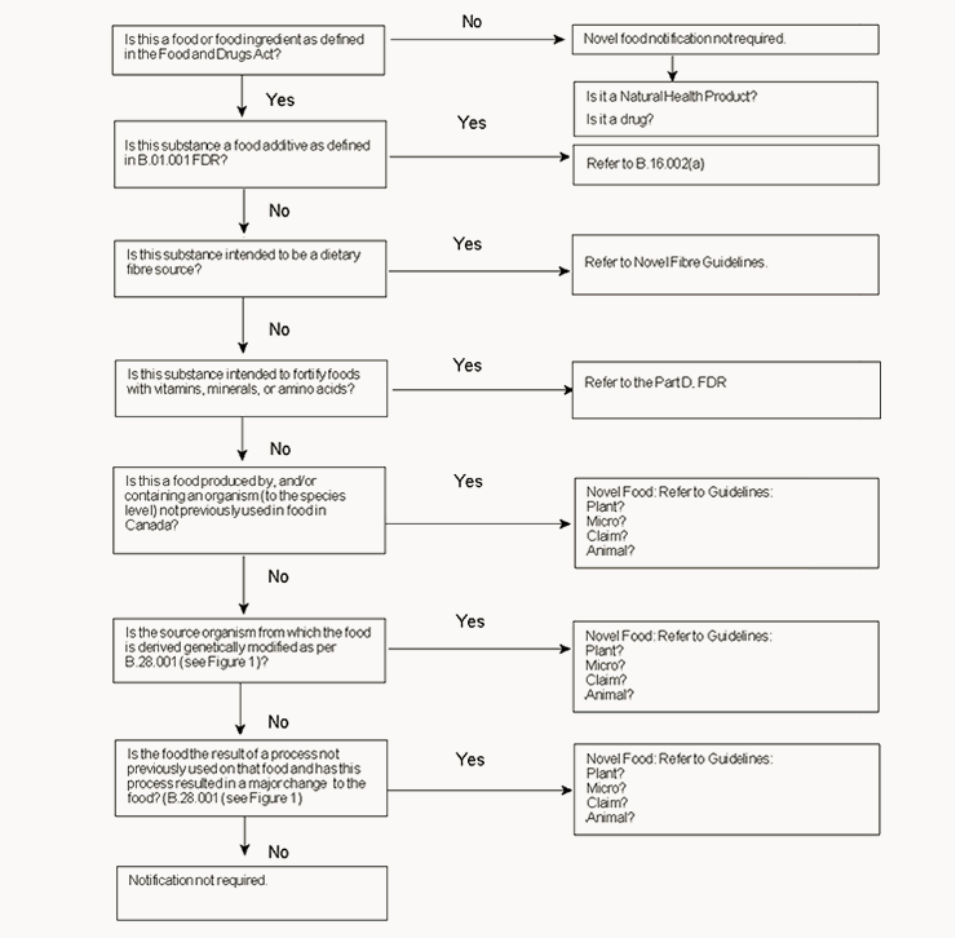

Figure 4: Decision tree for guidance on regulations or safety assessment guidelines for novel foods or similar products; Source: (Guidelines for the Safety Assessment of Novel Foods, 2006, pg 18).

7. Departments governing oversight of novel foods in Canada.

At the federal level, the responsibility of regulating foods including novel foods sold in Canada is shared by Health Canada and the Canadian Food Inspection Agency (CFIA). Health Canada is responsible for establishing policies and standards to govern safety and nutritional quality of foods as well as develop labelling policies related to health and nutrition (Health Canada). The CFIA primarily focuses on inspection and enforcement duties of the policies and guidelines that are set out by Health Canada. CFIA also monitors regulation of veterinary biologics, livestock feeds and fertilizers (CFIA, 2018). Environment Canada is responsible for assessing the impact the novel food has on the environment (Environment Canada, 2018). Agriculture and Agri-food Canada is responsible for supporting the growth and development of a competitive, innovative and sustainable Canadian agriculture and agri-food sector and for ensuring collaboration with its portfolio partners (HC, CFIA) which are also involved in regulating and supporting Canadian agriculture (AAFC, 2018).

Health Canada controls the sale of novel foods in Canada through a mandatory pre-market notification requirement which is outlined in Division 28 of part 2 of the Food and Drug Regulations. Under these regulations, manufacturers and importers are required to submit information to Health Canada regarding the novel product so that the safety aspects of the product can be assessed (Guidelines for the Safety Assessment of Novel Foods, 2006).

In the document titled "Guideline for the Safety Assessment of Novel Foods", the safety criteria were derived from a globally established scientific framework that was developed through the work and cooperation between the Organization for Economic Cooperation and Development (OECD), the Food and Agriculture Organisation (FAO), the World Health Organisation (WHO) and the Codex Alimentarius Commission. These guidelines provide for both the rigour and the flexibility required to determine the need for notification and to conduct the safety assessment of the broad range of food products being developed. This flexibility is needed to allow novel foods and food products to be assessed on a case-by-case basis and to take into consideration future scientific advances (Guidelines for the Safety Assessment of Novel Foods, 2006).

In the case of *in vitro* meat, Health Canada would participate in the assessment. The Canadian Food Inspection Agency, Environment Canada, Agriculture and Agri-food Canada and Health Canada would work together to assess the safety and nutrition of the final product (CFIA, 2012).

8. Introduction to "Guidelines for the Safety Assessment of Novel Foods".

> *This document encompasses novel foods, whether whole foods, food products, or food ingredients, that are derived from plant or microbial sources. Safety assessment criteria for novel foods derived from animals are under development. Manufacturers or importers of novel foods derived from animal sources should consult with the Food Directorate to discuss what information is appropriate to the evaluation of the safety of a particular product* (Guidelines for the Safety Assessment of Novel Foods, 2006).

Novel food safety assessments are conducted by the Food Directorate, Health Products and Food Branch of Health Canada. Guidelines are intended to provide assistance to the petitioner in order to prepare a novel food notification. It acts as a facilitator to ensure that the information provided by the petitioner is sufficient in order to conduct a safety assessment. Guidelines are not intended to explicitly define all the data required for conducting the safety assessment. Further data requirements could be identified on a case-by-case basis during the process of conducting the safety assessment. *In vitro* meat is one such product where the evaluation should occur on a separate basis of evaluation taking multiple factors involved in its manufacture and production into due consideration.

In this paper, Guidelines for plants and microorganisms will be used as a framework to suggest a model that can be adopted by petitioners intending to file a safety assessment for *in vitro* meat. However, the potential route of regulatory approval for *in vitro* meat will be explored considering two key factors:

1. *In vitro* meat technology is still under development and the technology that will be used for manufacturing the final product is unknown. This paper will consider key aspects derived from current literature and model the regulatory pathway based on current information which is available.

2.There are no guidelines for novel foods derived from animals, nor are there any recommended regulatory routes that *in vitro* meat technology can adopt. Considering this, the regulatory route suggested may vary depending on what method the manufacturer chooses to synthesise the final product and may involve additional or more stringent layers of scrutiny.

The current procedure for Approval of Novel Foods derived from Plants and Microorganisms requires a "Submission of a Novel Food Notification" and a "Submission of a Safety Assessment Data Package".

A notification by the manufacturer or importer, or the person authorized to sign on behalf of the manufacturer or importer shall include the following information:

Pre-market notification

Division 28 of Part B of the Food and Drug Regulations:

- *B.28.002. (1) No person shall sell or advertise for sale a novel food unless the manufacturer or importer of the novel food:*

  (a).has notified the Director in writing of their intention to sell or advertise for sale the novel food; and

  (b).has received a written notice from the Director under paragraph B.28.003(1)(a) or subsection B.28.003(2).

  (2) A notification referred to in paragraph (1)(a) shall be signed by the manufacturer or importer, or a person authorized to sign on behalf of the manufacturer or importer, and shall include the following information:

  (a)the common name under which the novel food will be sold;

  (b)the name and address of the principal place of business of the manufacturer and, if the address is outside Canada, the name and address of the principal place of business of the importer;

  (c)a description of the novel food, together with:

(i) information respecting its development,

(ii) details of the method by which it is manufactured, prepared, preserved, packaged and stored,

(iii) details of the major change, if any,

(iv) information respecting its intended use and directions for its preparation,

(v) information respecting its history of use as a food in a country other than Canada, if applicable, and

(vi) information relied on to establish that the novel food is safe for consumption;

(d) information respecting the estimated levels of consumption by consumers of the novel food;

(e) the text of all labels to be used in connection with the novel food; and

(f) the name and title of the person who signed the notification and the date of signing.

- *B.28.003. (1) Within 45 days after receiving a notification referred to in paragraph B.28.002(1)(a), the Director shall review the information included in the notification and :*

(a) if the information establishes that the novel food is safe for consumption, notify the manufacturer or importer in writing that the information is sufficient; or

(b) if additional information of a scientific nature is necessary in order to assess the safety of the novel food, request in writing that the manufacturer or importer submit that information.

(2) Within 90 days after receiving the additional information requested under paragraph (1)(b) the Director shall assess it and, if it establishes that the novel food is safe for consumption, notify the manufacturer or importer in writing that the information is sufficient (Food and Drugs Regulations CRC, c 870 – Novel Foods).

8.1 Applying the existing procedure to *in vitro* meat

Viewing point (2) in section B.28.002 under the lens of *in vitro* meat for pre-market notification:

a. The common name under which the novel food will be sold:

The common name under which *in vitro* meat will be sold depends upon the decision of the manufacturers in consultation with Health Canada. There is currently a debate over the definition challenge of *in vitro* meat which will be discussed later in the paper. The final decision taken over what the *in vitro* meat final product can be sold as lies with Health Canada.

b. The name and address of the principal place of business of the manufacturer and, if the address is outside Canada, the name and address of the principal place of business of the importer:

The manufacture would have to mention the details requested pertaining to their principal place of business.

c. A description of the novel food, together with

i. Information respecting its development:

According to current literature (Datar and Betti., 2010, Steinfeld et al., 2006, Stephens et al., 2018), there may be different routes that manufacturers may take during the development of *in vitro* meat. The variances may be the cell source, the culture media used, the variety of scaffold used and the bioreactor conditions besides various other components such as growth factors. Since this precise information is not generally available to the public due to intellectual property rights issues, it is mandatory that the manufacturers provide a detailed description of the process that they follow in order to synthesise *in vitro* meat.

ii. Details of the method by which it is manufactured, prepared, preserved, packaged and stored:

Manufacturers must comply with these requirements and furnish details regarding the process of manufacture, preparation details, how *in vitro* meat is preserved, packaged and stored in retail premises. The method to furnish these details is elucidated in the Submission of a Safety Assessment Data package section.

iii. Details of the major change:

The final product after it is synthesized must be compared to conventional meat and the major changes in terms of nutritional content, allergen information, toxicological, chemical and microbiological changes and any genetic variations must be stated clearly.

iv. Information respecting its intended use and directions for its preparation:

The directions for preparing *in vitro* meat final product along with the intended use and method of handling must be mentioned in the document.

v. Information respecting its history of use as a food in a country other than Canada, if applicable:

Since *in vitro* meat has not been legalised elsewhere in the world, it is not required to fill out this information.

vi. Information relied on to establish that the novel food is safe for consumption:

The manufacturers are responsible to submit the safety data assessment package of the final product.

d. Information respecting the estimated levels of consumption by consumers of the novel food:

Depending on what type of product is produced using the *in vitro* meat, the estimated levels of consumption of the product must be taken into consideration and subsequent analysis on whether it is safe to consume should be carried out.

e. The text of all labels to be used in connection with the novel food:

This should comply with the Consumer Packaging and Labelling Regulations in Canada and should be approved by Health Canada.

f. The name and title of the person who signed the notification and the date of signing:

The manufacturer must mention these details before submitting the final product for pre-market assessment.

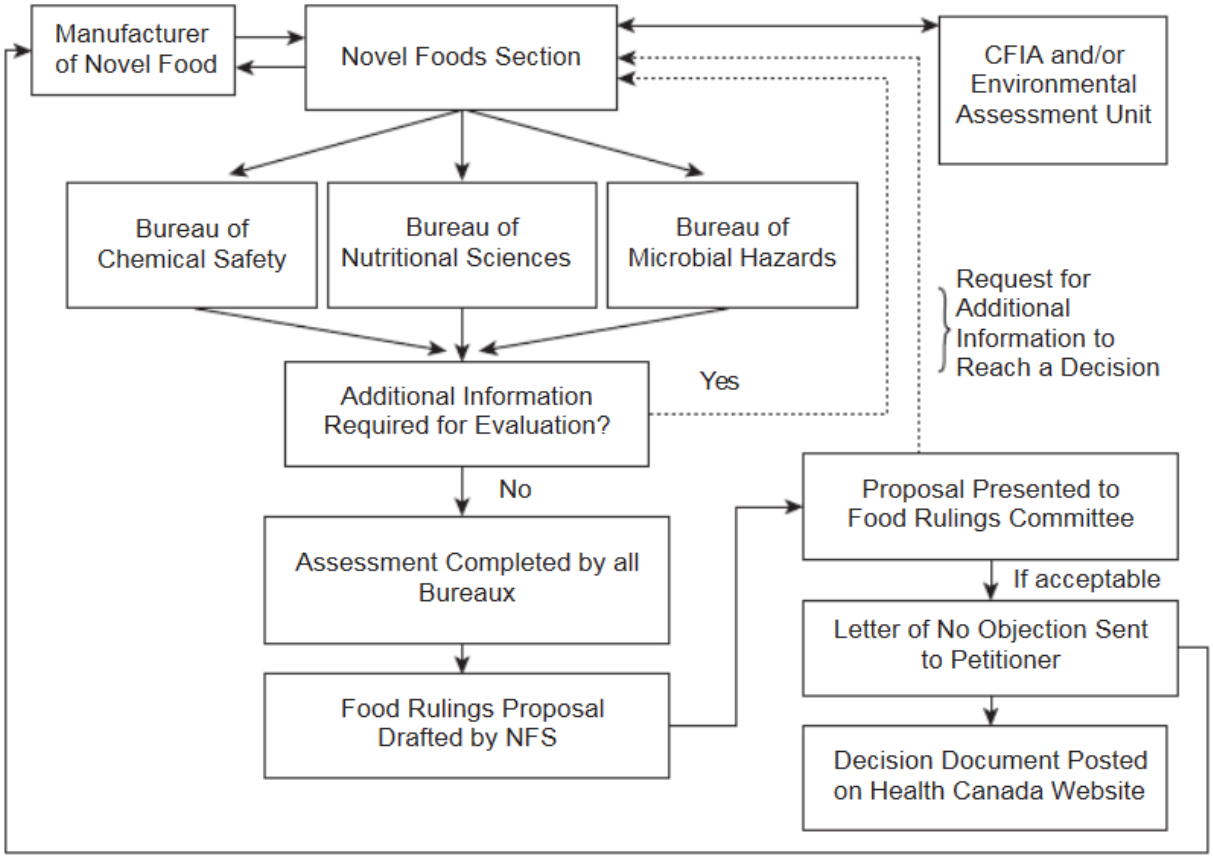

Figure 5: Processing a novel food notification and requests for additional information in the Food Directorate; Source: Guidelines for the Safety Assessment of Novel Foods, Health Canada, 2006, pg. 12.

9. Submission of a safety data assessment package.

When petitioners intend to submit data pertaining to their product, they must ensure that the experiments are conducted in accordance with scientific principles and if applicable, Good Laboratory Practice. If regulatory authorities request primary data, the information should be provided. The level of sensitivity of data should be documented and references to analytical methods must be made available. There is a great variety of potential novel foods, and for this reason, the application of Guidelines can vary on a case by case basis. In some cases, not all information may be required and in other cases, extra information may be necessary (Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 16).

Novel foods currently require the following information, based on whether the final product is a substance with no history of safe use, if it follows a novel process or if the product is an outcome of genetic manipulation.

Substance with No History of Safe Use

- History of use
- Dietary exposure
- Nutritional considerations
- Toxicology considerations
- Allergenicity considerations
- Chemical considerations

Novel Process

- Detail of novel process
- Dietary Exposure
- History of organism
- Nutritional considerations
- Toxicology considerations
- Allergenicity considerations
- Chemical considerations

Genetic Modification

- Characterization of derived line
- Genetic modification considerations
- History of organism (Host and Donor(s))
- Dietary exposure
- Nutritional considerations
- Toxicology considerations
- Allergenicity considerations
- Chemical considerations

(Source: Guidelines for the Safety Assessment of Novel Foods, Health Canada, 2006, pg. 19).

The safety assessment guidelines which are currently present for plants and microorganisms cannot be used directly to assess *in vitro* meat because the information in most of the assessment criteria is targeted specifically towards regulations of plants or microorganisms respectively. The regulatory framework would need to be honed to specifically scrutinise the various aspects of manufacturing *in vitro* meat and would also depend upon which method is employed by manufacturers.

Therefore, this paper will suggest an outline that can be used for regulating *in vitro* meat based on current literature.

10. Suggested outline for a safety assessment for *in vitro* meat.

10.1 Substance with no history of safe use

The *in vitro* meat production system consists of three components that have no previous history of safe use: scaffolds, culture media and oxygen carriers. An assessment of these components under

the safety assessment outline is as follows:

a. History of Use

i. Scaffold: Scaffold-based techniques can produce ground and boneless meat with soft consistency rather than highly structured meat like steaks (Bhat et al., 2015). Edelman et al. (2005) proposed beads made of edible collagen as a substrate and other possible scaffold structures include large elastic sheets or an array of long, thin filaments. Considering that the scaffold could possibly be made out of collagen, it is currently considered safe to consume in Canada according to Labelling Requirements for Meat and Poultry Products which mentions that "The use of edible wrappings (e.g. collagen or carrageenan) in the preparation of meat products other than sausages must be declared at the end of the ingredient list." (CFIA, 2018). However, since collagen has not been used in the capacity of a scaffold in order to produce meat, this paper argues that it must be considered as a product with no history of safe use or may also be qualified as a novel food additive and can undergo a safety assessment under the food additive framework. If the *List of Food Additives Permitted in Canada* do not allow for a particular use of a food additive, the manufacturer is required to file a food additive submission in accordance with Section B.16.002 of the Food and Drug Regulations before that food additive can be used in foods sold in Canada (Food and Drugs Regulations CRC, c 870).

ii. Culture Media: The culture media which is used for both stages of myosatellite cell development into skeletal cell is usually supplemented with 10%-20% growth media (Fujita, Endo, Shimizu, & Nagamori, 2010, Smith, Passey, Greensmith, Mudera, & Lewis, 2012). Horse serum or foetal calf serum is added to supplement the culture media (Chiron et al., 2012). New branded culture media which is devoid of animal serum such as Ultroser G or mushroom-derived serum can also be considered. Neither of these components have been used in manufacturing food, therefore they would have to undergo the safety assessment.

iii. Oxygen Carriers: Human hemoglobin has been produced by genetically modified plants (Dieryck et al., 1997) and microorganisms (Zuckerman, Doyle, Gorczynski, & Rosenthal, 1998). Microorganisms like *Escherichia coli* are already in use to produce human pharmaceuticals and food additives on a commercial scale and research is underway to determine if they can produce blood substitutes. Perfluorochemicals (PFCs) dissolve large volumes of oxygen and therefore can perform the same function as hemoglobin. (Lowe, 2006). Depending on the route of manufacture specific companies take in order to produce *in vitro* meat, the oxygen carrier would have to undergo a safety assessment based on where it is derived from or the method of production.

b. Dietary Exposure

The role of the dietary exposure assessment for substances with no history of use as foods intended for use as food is to estimate:

i. *How much of the food is likely to be consumed and at what frequency and what role it is likely to play in the diet (e.g. a significant protein source, a condiment, etc.);*

ii. *the potential impact of that food on the dietary intake of nutrients by combining the results of the findings in (a) with information on the nutrient composition of the food; and*

iii. *If there are any anti-nutrients, toxins, contaminants or novel substances determined to occur in the food, the potential exposure to those substances* (Section 4.1.1.2 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 22).

c. Nutritional Considerations

A guideline for producing data for nutritional considerations include:

i. *Function of the data to be submitted: The quality of data provided must be of sufficient quality and quantity to make an informed decision.*

ii. *Where published data on nutrient composition of the novel food are inadequate, analytical data may need to be obtained by the petitioner*

iii. *Nutrient composition such as proximate composition (i.e. ash, moisture, protein, fat, fibre, carbohydrate)*

iv. *Nutrient bioavailability: This pertains in particular to the evaluation of protein quality, the possibility of unknown anti-nutrients, and questions of nutrient bioavailability* (Section 4.1.1.3 in Guidelines for the Safety Assessment of Novel Foods, 2006, pages 24-26).

d. Toxicological considerations

This is required for foods with no history of safe use as some unknown hazard may be introduced into the food chain. Where it is not possible to identify novel components of the food, a case-by-case approach should be used to determine the appropriate toxicological tests to be carried out on the food (Section 4.1.1.4 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 27).

e. Allergenicity Considerations

The primary consideration in allergenicity assessment of a novel food is the prevention of unexpected and/or unavoidable exposure of susceptible individuals to food allergens. For foods with no history of safe use, the potential exists that one or more component proteins would have the capacity to cross-react with known food allergens or lead to the development of de novo hypersensitivity (Section 4.1.1.5 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg 28).

f. Chemical Considerations

> *The identification and levels of chemical contaminants must be reported in a food with no history of safe use. Potential levels and types of contaminants would be specific to the novel food type. It would therefore be necessary to determine the levels and ranges of contaminants which may be present in the food* (Section 4.1.1.6 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 28).

10.2 Novel Process

In an *in vitro* meat production system, a bioreactor ensures that cells are in near-continuous suspension in the culture media, fluid shear is maintained at low levels and tissue assemblies can be easily suspended. It scales up the cell-culturing process (Edelman et al. 2005). A bioreactor has never been used in food production in this capacity before, so the process would therefore be considered novel. An ideal bioreactor should have integrated, closed systems which increase automation and reduce errors and contamination risk (Specht et al., 2018).

a. Details of the Novel Process

The process of culturing cells in a bioreactor as opposed to growing an animal and slaughtering it for meat is a novel process. The cells are cultured in a bioreactor which should, preferably, have in-line monitoring of media components to adjust the media perfusion in real time. The bioreactor should have a large volume to produce high yields of cells and a highly automated system (Specht et al., 2018). The objective of using a bioreactor for cell culturing is to allow medium perfusion. For large scale operations, the bioreactor is a very important requirement since the cells would require a large, enclosed surface area for culturing and proliferation (Bhat & Bhat, 2011). It would also fulfill the role of promoting tissue growth by creating an ambient environment.

b. Dietary Exposure

> *In cases where the nutrient composition of food has been altered, either intentionally or unintentionally, through the novel process, the magnitude of that change should be assessed against the expected nutritional value of the unprocessed food and/or against the changes that result from conventional processes used on the same food, and also to determine if it would have a significant impact on overall dietary nutrient intakes for consumers. The final product obtained through cell culturing would have to be tested against conventional meat and the differences in properties must be analysed* (Section 4.1.2.2. in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 30).

c. Nutritional Considerations

> *A full description of the novel process, the purpose of the process, and the food product on which it could be applied:*

i. *A complete description of the experimental design, experimental conditions, and how sources of variation for nutrient levels were controlled.*

ii. *A complete description of sample collection and sample preparation.*

iii. *A citation and/or description of the analytical and statistical methods used to obtain data for the nutritive and non-nutritive components.*

iv. *Results of statistical analyses.*

v. *Raw data for all components analysed.*

vi. *Published data if available.*

vii. *intended use of the product as food in Canada, i.e. ingredient type(s), possible end products, level of use if different from current products which it would replace, known patterns of use and consumption of the food and its derivatives.*

viii. *any foreseeable unintended uses* (Section 4.1.2.4 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 36).

d. Toxicological Considerations

Depending on these determinations, conventional studies of toxicity, including assays of metabolism, toxicokinetics, chronic toxicity/carcinogenicity, impact on reproductive function, and teratogenicity, may need to be performed on the final food product or its components as appropriate (Section 4.1.2.5 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 40).

e. Allergenicity Considerations

In cases where the application of a novel process to a food results in the generation of a novel protein or an alteration of the protein content of a food containing allergenic proteins, a consideration of the allergenic potential of the novel food would be required. In this case, it is not required (Section 4.1.2.6 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 41).

f. Chemical Considerations

The identification and levels of chemical contaminants must be reported. Contaminants could be naturally present in the food before application of the novel process or could be introduced as a result of application of the novel process. It would be necessary to provide a comparison of the levels of chemical contaminants in the novel food with those levels typically found in the food product prepared by accepted traditional processes (Section 4.1.2.7 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 41).

Good Manufacturing Practises could be adhered to during the process of synthesising cells using a bioreactor to apply an added layer of scrutiny to the process. Health Canada has enlisted Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001) to promote good nutrition and informed usage of food, drugs and natural health products in order to maximize the safety and efficacy of foods and drugs for human consumption (Health Canada, 2011)**.**

10.3 Genetic Modification

Genetic engineering may be used in cell culturing in order to create meat products with different textural, taste and flavour profiles. In theory, using embryonic stem cells as opposed to myosatellite stem cells enables cells to have unlimited regenerative potential which eliminates the need to harvest more embryos. However, the slow accumulation of genetic mutations may occur overtime with embryonic stem cells. An *in vitro* meat production system requires multiple cell divisions to form a cell culture mass and muscle tissue (Datar and Betti, 2010). In order to overcome this issue, Edelman et al., in 2005 suggested putting forth three strategies of overcoming the issue:

1. Regularly replenishing the cell culture.

2. Using an immortal cell line.

3. Immortalizing a cell line.

Most cells that are used for this process would require regularly replenishing the cell line and embryonic stem cells satisfy the second point. The third strategy which requires genetic manipulation may, however, lead to further difficulties in public acceptance and controversies. (Edelman et al., 2005).

a. Characterisation of derived line

The approach of the safety assessment is based on the principle that the safety of novel products is assessed relative to a conventional counterpart having a history of safe use, taking into account both intended and unintended effects. Any significant differences between the novel and the conventional strain are then assessed for potential adverse health effects. Of particular interest to the safety assessment is whether the modification could inadvertently develop or increase the pathogenicity, toxicity, or allergenicity potential of an organism (Section 4.1.3.1 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 44).

The cell line which is genetically modified may be compared to a cell line derived from an animal without genetic modification and the differences are assessed for potential adverse health effects.

b. Genetic modification considerations

Cells would potentially be modified by modern genetic engineering techniques, in which case, two important points must be mentioned:

i. Description of the genetic modification(s)

The description of the modification process should include:

- *Information on the method(s) of modification used, description and characterization of all genetic material potentially delivered, if applicable, including the source, identity and expected function in the organism; and*
- *Details of manipulations or modifications to introduced, intermediate and recipient genetic material (e.g. changes that affect the amino acid sequence of expression product).*
- *Information should be provided on DNA added, inserted, deleted, or modified, including:*
- *The characterization of all the genetic components including marker genes, regulatory and other elements affecting the function of the DNA;*
- *the size and identity;*
- *the location and orientation of the sequence in the final vector/construct; and*

Function in the organism (Section 4.1.3.2 in Guidelines for the Safety Assessment of Novel Foods, 2006, pages 44-46).

ii. Characterization of the genetic modification(s):

Information should be provided on DNA insertions into the genome as well as expressed substances on the modified cell (Section 4.1.3.2 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 46).

c. History of organisms (Host and Donor(s))

The history of both donor and host organisms can provide information that is important to the assessment of a novel food (Section 4.1.3.3 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 48). Adhering to this condition would depend on whether a donor and host are used in order to create the cell line for *in vitro* meat production, which would depend upon the manufacturer.

d. Dietary Exposure

If the nutrient composition of food has been altered through genetic modification, the magnitude of the alteration should be assessed against the nutritional value of the conventional food. A decision to conduct a full exposure assessment may be done by intake modelling using

current dietary intake databases, preferably using data for Canadian subjects in which the novel food is replaced with the unmodified or conventional food (Section 4.1.3.4 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg 48).

e. Nutritional Considerations

Data should be provided for the raw food and data may also be required for food prepared for human consumption. The effects of processing, storage and cooking should examine the effectiveness of cooking to destroy anti-nutrients, in cases where anti-nutrients are normally destroyed by cooking (Section 4.1.3.5 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 51).

f. Toxicological Considerations

These must cover novel substances like new proteins which may be formed or unintended effects that may arise due to consumption of the final product (Section 4.1.3.6 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 59).

g. Allergenicity Considerations

Drawing from the assessment strategy for plants, which may be correlated to testing *in vitro* meat involves an initial assessment that requires identifying the source of protein, assessing the amino acid sequence homology, pepsin resistance, specific serum screening, areas requiring further development and finally any unintended effects that may have been caused on endogenous allergens (Section 4.1.3.7 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 61).

h. Chemical Considerations

The identification and levels of chemical contaminants must be reported. Potential levels and types of contaminants would, of course, be specific to the food to be modified and, also, the type of process employed to achieve the genetic modification. Any food additives present in the final food (e.g. anticaking agents, carrier solvents, solid diluents, colours, preservatives) or processing aids used during the course of manufacture of the food (e.g. precipitation aids, filtering agents, etc.) should be identified and their levels indicated. In the case of novel foods intended for use as ingredients in other foods, specifications of identity and purity should be provided, along with a sample label and Directions for Use (Section 4.1.3.8 in Guidelines for the Safety Assessment of Novel Foods, 2006, pg. 61).

11. Conclusion

In vitro meat production is real but nascent. The bigger question is not "can we do it" but "how will we regulate it"? This article reviews the current technology which is in place to synthesise *in vitro* meat and address how the technology might be regulated in Canada.

In vitro meat may be regulated as a novel food since it falls into the three domains of novel food classification according to the Food and Drugs Regulations: no history of safe use, novel process and potentially genetically modified. This article demonstrates that the existing Guidelines for Novel Foods in Canada are flexible and accommodative of new technologies. The roadmap for the future must involve further technical research, a multi-stakeholder perspective to the challenges that this technology faces and a tight regulatory framework which has a comprehensive oversight of the manufacturing, storage, distribution and retail of *in vitro* meat and its products.

While *in vitro* meat production is an emergent technology which is gaining a lot of traction due to the potentially unique benefits it possesses, consumer acceptance remains the wild card in seeing this technology expand.

12. References

Aleph Farms Ltd. (2018). Aleph Farms to the USDA: Clean Meat Can Improve Food Safety. Retrieved from https://www.prnewswire.com/news-releases/aleph-farms-to-the-usda-clean-meat-can-improve-food-safety-300665522.html.

Alexandratos, N., & Bruinsma, J. (2012). World agriculture towards 2030/2050: the 2012 revision (Vol. 12, No. 3). FAO, Rome: ESA working paper. Available at: http://www.fao.org/docrep/016/ap106e/ap106e.pdf.

Benjaminson, M., Gilchriest, J., and Lorenz, M. (2002). *In vitro* edible muscle protein production system (MPPS): Stage 1, fish. Acta Astronaut. 51, 879.

Bhat ZF, Bhat H .(2011). Tissue engineered meat- future meat. J Stored Prod Postharvest Res 2:1–10.

Bhat, Z., Kumar, S., & Fayaz, H. (2015). *In vitro* meat production: Challenges and benefits over conventional meat production. Journal Of Integrative Agriculture, 14(2), 241-248. doi: 10.1016/s2095-3119(14)60887-x.

Bian, W., & Bursac, N. (2009). Engineered skeletal muscle tissue networks with controllable architecture. Biomaterials, 30, 1401–1412.

Birkenhead, Smith FE. (1930). In: Earl of. The world in 2030 A.D, vol 1930. Hodder and Stoughton, London.

Burattini, S., Ferri, P., Battistelli, M., Curci, R., Luchetti, F., & Falcieri, E. (2004). C2C12 murine myoblasts as a model of skeletal muscle development: Morpho-functional characterization. European Journal of Histochemistry, 48, 223–233.

Butler, M. (2015). Serum and protein free media. Animal Cell Culture, 9, 223–236.

CBC News. Ranchers and vegans in war of words over what to call lab-grown meat (2018). Retrieved from https://www.cbc.ca/news/technology/lab-meat-wording-1.4712839.

CDC (Centre for Disease Control). (2012). CDC estimates of foodborne illness in the United States. [2014-5-13]. http:// www.cdc.gov/foodborneburden/2011-foodborne-estimates.html.

CFIA. (2012). Animal Biotechnology - Roles and Responsibilities of the Government of Canada - Canadian Food Inspection Agency. Retrieved from http://www.inspection.gc.ca/animals/animal-biotechnology/roles-and-responsibilities/eng/1334783323017/1375568214394.

CFIA. (2015). CFIA at A Glance - Canadian Food Inspection Agency. Retrieved from http://www.inspection.gc.ca/about-the-cfia/organizational-information/at-a-glance/eng/1358708199729/1358708306386.

CFIA. (2018). Labelling Requirements for Meat and Poultry Products - Food - Canadian Food Inspection Agency. Retrieved from http://www.inspection.gc.ca/food/labelling/food-labelling-for-industry/meat-and-poultry-products/eng/1393979114983/1393979162475?chap=0.

Chan, B., & Leong, K. (2008). Scaffolding in tissue engineering: general approaches and tissue-specific considerations. European Spine Journal, *17*(S4), 467-479. doi: 10.1007/s00586-008-0745-3.

Chen, S., Nakamoto, T., Kawazoe, N., & Chen, G. (2015). Engineering multi-layered skeletal muscle tissue by using 3D microgrooved collagen scaffolds. Biomaterials, 73, 23–31.

Chiron, S., Tomczak, C., Duperray, A., Lainé, J., Bonne, G., Eder, A., et al. (2012). Complex interactions between human myoblasts and the surrounding 3D fibrin-based matrix. PLoS One, 7, e36173.

Churchill W. (1932). Fifty years hence. In: Thoughts and Adventures London: Thornton Butterworth pp 24–27.

Coecke, S., Balls, M., Bowe, G., Davis, J., Gstraunthaler, G., Hartung, T., et al. (2005). Guidance on good cell culture practice: A report of the second ECVAM Task Force on good cell culture practice. Alternatives to Laboratory Animals, 33(3), 261−287.

Cosgrove, E. (2018). BREAKING UPDATE: Memphis Meats Adds Tyson to Investor List With Cargill, Gates, Branson, Musk, more - AgFunderNews. Retrieved from https://agfundernews.com/memphis-meats-raises-17m-series-cargill-gates-branson-musk.html

Datar, I., & Betti, M. (2010). Possibilities for an *in vitro* meat production system. Innovative Food Science & Emerging Technologies, 11(1), 13-22. doi: 10.1016/j.ifset.2009.10.007.

Dieryck, W., Pagnier, J., Poyart, C., Marden, M., Gruber, V., & Bournat, P. et al. (1997). Human haemoglobin from transgenic tobacco. *Nature*, *386*(6620), 29-30. doi: 10.1038/386029b0.

Edelman P D .(2003). *In vitro* meat production. http://new-harvest.org/wp-content/uploads/2013/03/Edelman.pdf.

Edelman, P. D., McFarland, D. C., Mironov, V. A., & Matheny, J. G. (2005). *In vitro* cultured meat production. Tissue Engineering, 11(5), 659−662.

Edney, A. (2018). Lab-Grown Meat Startups Backed by Bill Gates, Tyson Foods Face FDA Oversight. Retrieved from https://www.bloomberg.com/news/articles/2018-06-15/lab-grown-meat-backed-by-gates-tyson-foods-faces-u-s-oversight.

Egbert, R & Borders, C. (2006). Achieving success with meat analogs. Food technology. 60. 28-+.

Engler, A. J., Griffin, M. A., Sen, S., Bönnemann, C. G., Sweeney, H. L., & Discher, D. E. (2004). Myotubes differentiate optimally on substrates with tissue-like stiffness, pathological implications for soft or stiff microenvironments. Journal of Cell Biology, 166(6), 877−887.

FAO (2006). Livestock's long shadow— Environmental issues and options. : FAO publications.

FAO. (2009). How to Feed the World in 2050?. Retrieved from http://www.fao.org/fileadmin/templates/wsfs/docs/expert_paper/How_to_Feed_the_World_in_2050.pdf.

Food and Drugs Regulations, Division 16, B.16.002 – Food Additives.

Food and Drugs Regulations, Division 28, B.28.001- Novel Foods.

Fortune, A. (2018). Clean meat definition top of US beef producer priorities. Retrieved from https://www.globalmeatnews.com/Article/2018/02/14/Clean-meat-definition-top-of-US-beef-producer-priorities.

Froud, S. J. (1999). The development, benefits and disadvantages of serum-free media. Developments in Biological Standardization, 99, 157−166.

Fujita, H., Endo, A., Shimizu, K., & Nagamori, E. (2010). Evaluation of serum-free differentiation conditions for C2C12 myoblast cells assessed as to active tension generation capability. Biotechnology and Bioengineering, 107, 894–901.

Guidelines for the Safety Assessment of Novel Foods, Health Canada. (2006). Guidelines for the Safety Assessment of Novel Foods - Canada.ca. Retrieved from https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidelines-safety-assessment-novel-foods-derived-plants-microorganisms/guidelines-safety-assessment-novel-foods-2006.html.

Hawks, C. (2018). How close are we to a hamburger grown in a lab? Retrieved from https://www.cnn.com/2018/03/01/health/clean-in-vitro-meat-food/index.html.

Health Canada. (2011). Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001) - Canada.ca. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-

health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/good-manufacturing-practices-guidelines-2009-edition-version-2-0001.html.

Hinds, S., Bian, W., Dennis, R. G., & Bursac, N. (2011). The role of extracellular matrix composition in structure and function of bioengineered skeletal muscle. Biomaterials, 32, 3575–3583.

Hocquette, J. (2016). Is *in vitro* meat the solution for the future? Meat Science, 120, 167-176. doi: 10.1016/j.meatsci.2016.04.036.

Kadim, I., Mahgoub, O., Baqir, S., Faye, B., & Purchas, R. (2015). Cultured meat from muscle stem cells: A review of challenges and prospects. Journal Of Integrative Agriculture, 14(2), 222-233. doi: 10.1016/s2095-3119(14)60881-9.

Kosnik, P.E., Dennis, R.G., and Vandenburgh, H.H. (2003). Tissue engineering skeletal muscle. In: Guilak, F., ed. Functional Tissue Engineering. New York: Springer-Verlag pp. 377–392.

Laestadius, L., & Caldwell, M. (2015). Is the future of meat palatable? Perceptions of *in vitro* meat as evidenced by online news comments. Public Health Nutrition, 18(13), 2457–2467.

Lowe, K. (2006). Blood substitutes: From chemistry to clinic. Journal of Materials Chemistry, 16(43), 4189−4196.

Marques, A., Lourenço, H., Nunes, M., Roseiro, C., Santos, C., & Barranco, A. et al. (2011). New tools to assess toxicity, bioaccessibility and uptake of chemical contaminants in meat and seafood. Food Research International, 44(2), 510-522. doi: 10.1016/j.foodres.2010.12.003.

Martin I, Wendt D, Heberer M .(2004). The role of bioreactors in tissue engineering. Trends Biotechnology 22:80.

Mattick, C. S., Landis, A. E., Allenby, B. R., & Genovese, N. J. (2015). Anticipatory life cycle analysis of *in vitro* biomass cultivation for cultured meat production in the United States. Environmental Science & Technology, 49(19), 11941–11949.

McFarland, D.C. (1999) Influence of growth factors on poultry myogenic satellite cells. Poultry Sci. 78, 747.

Mudera, V., Smith, A. S., Brady, M. A., & Lewis, M. P. (2010). The effect of cell density on the maturation and contractile ability of muscle derived cells in a 3D tissue-engineered skeletal muscle model and determination of the cellular and mechanical stimuli required for the synthesis of a postural phenotype. Journal of Cellular Physiology, 225, 646–653.

New Food Magazine. (2018). Cultured meat firm highlights safety advantages in U.S. labelling debate. Retrieved from https://www.newfoodmagazine.com/news/67657/cultured-meat-labelling/.

O'Riordan, K., Fotopoulou, A., & Stephens, N. (2017). The first bite: Imaginaries, promotional publics and the laboratory grown burger. Public Understanding of Science, 26(2), 148–163.

PHAC. (2018). Public Health Notice - Outbreak of Salmonella infections linked to frozen raw breaded chicken products - Canada.ca. Retrieved from https://www.canada.ca/en/public-health/services/public-health-notices/2017/outbreak-salmonella-infections-linked-to-frozen-raw-breaded-chicken-products.html

Pimentel, D., & Pimentel, M. (2003). Sustainability of meat-based and plant-based diets and the environment. The American Journal of Clinical Nutrition, 78(3 Suppl), 660S–663S.

Poinski, M. (2018). How should the FDA regulate lab-grown meat? Retrieved from https://www.fooddive.com/news/how-should-the-fda-regulate-lab-grown-meat/527715/.

Post, M. (2012). Cultured meat from stem cells: Challenges and prospects. Meat Science, *92*(3), 297-301. doi: 10.1016/j.meatsci.2012.04.008.

Powell, C.A., Smiley, B.L., Mills, J., and Vandenburgh, H.H. (2002) Mechanical stimulation improves tissue-engineered human skeletal muscle. Am. J. Physiol. Cell Physiol. 283, C1557.

Purdy, C. (2017). In four years, the price of lab-grown “meat” has fallen by 96%. There’s still a long way to go. Retrieved from https://qz.com/997565/in-four-years-the-price-of-lab-grown-meat-has-fallen-by-96-theres-still-a-long-way-to-go/.

Radisic, M., Euloth, M., Yang, L., Langer, R., Freed, L. E., & Vunjak-Novakovic, G. (2003). High-density seeding of myocyte cells for cardiac tissue engineering. Biotechnology and Bioengineering, 82(4), 403−414.

Rohter, L. (2003). Relentless Foe of the Amazon Jungle: Soybeans. Retrieved from https://www.nytimes.com/2003/09/17/world/relentless-foe-of-the-amazon-jungle-soybeans.html.

Sakar, M., Neal, D., Boudou, T., Borochin, M., Li, Y., & Weiss, R. et al. (2012). Formation and optogenetic control of engineered 3D skeletal muscle bioactuators. Lab On A Chip, 12(23), 4976. doi: 10.1039/c2lc40338b.

Shammas, M. A. (2011). Telomeres, lifestyle, cancer, and aging. Current Opinion in Clinical Nutrition and Metabolic Care, 14(1), 28–34.

Shapiro, P. (2018). One order of eggs, hold the hens: How acellular agriculture will reshape food.

Retrieved from https://www.fooddive.com/news/one-order-of-eggs-hold-the-hens-how-acellular-agriculture-will-reshape-fo/524943/.

Sharma, S., Thind, S., & Kaur, A. (2015). *In vitro* meat production system: why and how? Journal Of Food Science And Technology, 52(12), 7599-7607. doi: 10.1007/s13197-015-1972-3.

Smetana, S., Mathys, A., Knoch, A., & Heinz, V. (2015). Meat Alternatives: Life cycle assessment of most known meat substitutes. International Journal of Life Cycle Assessment, 20, 1254–1267.

Smith, A. S., Passey, S., Greensmith, L., Mudera, V., & Lewis, M. P. (2012). Characterization and optimization of a simple, repeatable system for the long term *in vitro* culture of aligned myotubes in 3D. Journal of Cellular Biochemistry, 113, 1044–1053.

Snyman, C., Goetsch, K. P., Myburgh, K. H., & Niesler, C. U. (2013). Simple silicone chamber system for *in vitro* three-dimensional skeletal muscle tissue formation. Frontiers in Physiology, 4, 349.

Specht, E., Welch, D., Rees Clayton, E., & Lagally, C. (2018). Opportunities for applying biomedical production and manufacturing methods to the development of the clean meat industry. Biochemical Engineering Journal, 132, 161-168. doi: 10.1016/j.bej.2018.01.015.

Steinfeld H, Gerber P, Wassenaar T, Castel V, Rosales M, De Haan C. (2006). Livestock's Long Shadow: Environmental Issues and Options. FAO 978-92-5-195571-7. Information Division, Rome, Italy.

Stephens, N., Di Silvio, L., Dunsford, I., Ellis, M., Glencross, A., & Sexton, A. (2018). Bringing cultured meat to market: Technical, socio-political, and regulatory challenges in cellular agriculture. Trends in Food Science & Technology, 78, 155-166. doi: 10.1016/j.tifs.2018.04.010.

Tuomisto, H., & Teixeira de Mattos, M. (2011). Environmental Impacts of Cultured Meat Production. Environmental Science & Technology, *45*(14), 6117-6123. doi: 10.1021/es200130u.

US Cattlemen's Association. (2018). Petition for the imposition of beef and meat labelling requirements. Retrieved from https://www.fsis.usda.gov/wps/wcm/connect/e4749f95-e79a-4ba5-883b-394c8bdc97a3/18-01-Petition-US-Cattlement-Association020918.pdf?MOD=AJPERES347e04b68da1/?noredirect=on&utm_term=.ba513d355a58.

Watson, E. (2018). Memphis Meats: 'What's common in Silicon Valley is that you move fast and break things, but that's an awful way to approach making food'. Retrieved from https://www.foodnavigator-usa.com/Article/2018/05/02/Memphis-Meats-VP-Science-does-not-occur-in-a-cultural-vacuum.

Waughray, D. (2018). Meat: the Future Time for a Protein Portfolio to Meet Tomorrow's Demand. Retrieved from: http://www3.weforum.org/docs/White_Paper_Meat_the_Future_Time_Protein_Portfolio_Meet_Tomorrow_Demand_report_2018.pdf.

Williamson M. (2003). Space ethics and the protection of the space environment. Science Policy, 19, 47‑52.

Wilks, M., & Phillips, C. (2017). Attitudes to *in vitro* meat: A survey of potential consumers in the United States. PLoS One, 12(2), e0171904.Yuge, L., and Kataoka, K. (2002) Differentiation of myoblasts accelerated in culture in a magnetic field. *In vitro* Cell. Dev. Biol. Anim. 36, 383.

Zuckerman, S., Doyle, M., Gorczynski, R., & Rosenthal, G. (1998). Preclinical Biology of Recombinant Human Hemoglobin, Rhb1.1. Artificial Cells, Blood Substitutes, And Biotechnology, 26(3), 231-257. doi: 10.3109/10731199809117456.