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ANALYSIS OF LAWS GOVERNING COMBINATION PRODUCTS, TRANSGENIC FOOD, PHARMACEUTICAL PRODUCTS AND THEIR APPLICABILITY TO EDIBLE VACCINES

Simon Maxwell¹

Developments in the field of public safety during the early twentieth century culminated in the passing of the milestone Federal Food, Drug, and Cosmetic Act (FFDCA) in 1938.² The FFDCA ushered in a new era of legal precedent that requires companies to submit their products to a pre-market evaluation. This evaluation comprises in-depth analyses that ensure applicant products are safe, pure, accurately labeled, and dosage-standardized to preserve both consumer health and product integrity.

The FFDCA resulted in the creation of the Food and Drug Administration (FDA) to perform these pre-market evaluations. The original incarnation of the FDA had only three regulatory divisions that specialized in reviewing either (1) foods, (2) drugs, or (3) cosmetics. As medical and industrial innovation broadened the scope of applicative technologies, the FFDCA saw various amendments that expanded the FDA's authority to include control over medical devices (including radiation-emitting products) and dietary supplements.

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2 John P. Swann, *FDA's Origin*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm> (last updated Jan. 23, 2014).

They also widened food's categorical domain to include pesticide residues, food additives, and color additives.³

As technological innovation develops more effective forms of treatment, new types of products will exceed current FDA categorizations. Combination products, for instance, represent a continuum of development; different types of products are combined to strengthen treatment, minimize side effects, and reduce pill burden. Combination products were officially addressed in 1990 when the FFDCA was amended to address the legal ambiguities found in regulating products that potentially represented a combination of a drug, device, or biological product.⁴

Since then, the classification of combination products has become increasingly popular among regulatory officials. Within two decades, the combination product market has expanded to include "drug eluting stents, infusion pumps, bone graft implants, photodynamic therapy, wound care combination devices, inhalers, transdermal patches and others including intraocular implants and drug eluting beads."⁵ The drug-device combination products market is expected to reach 115.1 billion dollars in 2019, effectively becoming the new standard in medical treatment.⁶

This rapid proliferation of combination products has placed significant pressure upon the FDA to develop a reliable regulatory policy that ensures combination product safety. Despite useful attempts made to classify and regulate them, combination products represent

3 John P. Swann, *FDA History-Part III*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm055118.htm> (last updated June 18, 2009).

4 Suzanne O'Shea, *Working Through the US Rules for Combination Products*, Reg. Aff. J. Pharma 651, 651 (Oct. 16, 2008).

5 *Drug Device Combination Products Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013–2019*, Transparency Market Research, PR NEWswire (Dec 24, 2013), <http://www.prnewswire.com/news-releases/drug-device-combination-products-market-is-expected-to-reach-usd-1151-billion-globally-in-2019-transparency-market-research-237136721.html>.

6 *Id.*

a significant portion of FDA recalls within the past two decades.⁷ Section I will examine the unique challenges these products pose to regulatory agencies.

In response to these challenges, the FDA has attempted to develop an algorithm to assign appropriate regulation. This algorithm is based on evaluating the safety of a product as a whole, and it necessitates a collaborative effort by multiple component agencies.⁸ Section II will discuss current laws regulating combination products and how the FDA ensures their safety.

However, despite adopting increasingly sophisticated methods, certain products continue to defy classification within existing regulatory framework. The combination product category is currently limited to combinations composed of drugs, devices, or biologics, which excludes broad classes of products that are also under the regulatory domain of the FDA, including food and cosmetics. This means that a large class of potential products still has no applicable regulation within a field where FDA regulation assignments remain highly interpretive and controversial.⁹ Products that highlight this deficiency are genetically-modified, edible vaccines. These edible vaccines are fruits and vegetables that have been genetically engineered to naturally produce proteins that generate an immune-response when eaten. These vaccine foods do not require refrigeration or specialized equipment like traditional vaccines, and they can be grown indigenously, thus eliminating the need for expensive transportation. These products have the potential to greatly improve the quality of life of millions by providing them a cheap, effective form

7 *Recalls, Market Withdrawals, & Safety Alerts*, U.S. FOOD AND DRUG ADMINISTRATION (Mar. 04, 2014), <http://www.fda.gov/safety/recalls/>.

8 Definition of Primary Mode of Action of a Combination Product, 60 Fed. Reg. 49,848, 49,857 (Aug. 25, 2005) (to be codified at 21 C.F.R. pt. 3).

9 *Other Types of Combinations of FDA Regulated Products*, U.S. FOOD & DRUG ADMIN. (Mar. 30, 2009), <http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101464.htm>.

of preventative care against diseases, including Hepatitis B, which infects up to one third of the population in some areas of the world.¹⁰

Section III argues that the combination product definition should be expanded to include food-biologic products so that edible vaccines, specifically the banana-vaccine, can be effectively regulated as such. In addition, it argues that the unique properties associated with food-biologic products warrant the creation of additional legislation, so that they may be safely commercialized and made available to the public.

I. CHALLENGES POSED BY COMBINATION PRODUCTS

According to the FFDCA, all products evaluated by the FDA are subject to a regulatory assessment. This assessment must adequately ensure that the admission of these products into interstate commerce does not represent the introduction or delivery “of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.”¹¹ The term *adulterated* refers to any product that might pose a significant threat to human health, and *misbranded* refers to any product whose label is misleading or insufficient in characterizing the product in any way.¹² These legal definitions are very broad, and the FDA has developed a wide range of regulations to satisfy these requirements.

While all products regulated by the FDA are subject to these standards, regulation is different from product to product. For example, a medical device must comply with various installation and op-

10 Qingxian Kong, Liz Richter, Yu Fang Yang, Charles J. Arntzen, Hugh S. Mason, & Yasmin Thanavala, *Oral Immunization With Hepatitis B Surface Antigen Expressed In Transgenic Plants*, 98 PROC. NAT’L ACAD. SCI. U.S. 11539, 11539 (September 25, 2001) [hereinafter Kong et al., *Oral Immunization*].

11 Within the FFDCA, “drugs” is an umbrella term for both drugs and biological products. The specific definition and regulation associated with biological products is found within 42 USC § 262; 21 U.S.C. §331(b) (2010).

12 *See Id.* § 351; *See Id.* § 352.

eration requirements to be considered free of *adulteration*.¹³ Drugs, by comparison, must ensure accurate dosage and purity.¹⁴ Ultimately, adulteration is determined relative to what is being assessed.

In response, the FDA comprises several sub-departments that specialize in a particular class of product, including the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH). Historically, obvious differences in product type have made it simple to delegate to these sub-departments.

Today, however, advances in the fields of nanotechnology, material engineering, genetic engineering, and molecular biology have resulted in the creation of combination products, which blur the distinction between previously neat categories of regulation. For example, how does one regulate a contact lens (a medical device) that has been combined with a drug to treat glaucoma? This product is potentially subject to both drug and medical device regulation for which there is no immediate, specialized category, i.e., a drug, biologic, cosmetic, food item, or medical device. This poses a unique challenge to FDA officials who must ensure the safety of the product so they can legally introduce it into interstate commerce. According to the FDA website, combination products have the potential to “impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications.”¹⁵ Because of the challenges they pose, these products need to be effectively characterized to address the practical challenges of regulation.

Combination products are defined within the FFDCA as products composed of two or more regulated articles that have been com-

13 *See Id.* § 352(h).

14 *See Id.* § 352(b).

15 *About Combination Products*, U.S. FOOD & DRUG ADMIN. (Oct. 20, 2009), <http://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm>.

bined as a single entity, or items that consist of two or more different regulated products (either a drug, device, or biologic) that have been specifically designed so they must be used together to achieve the ultimate intended effect. A combination product can be composed of “any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.”¹⁶ Examples include insulin injector pens, metered dose inhalers, condoms with spermicide, implants with growth factors, or light-activated drugs with their laser accompaniments.

While this definition limits combination products to being composed exclusively of drugs, devices, and biologics, other types of combinations potentially pose similar regulatory issues, and currently, there is no set regulatory pathway they can be expected to follow. These kinds of products may include combinations of drugs, devices, and/or biological products with other types of FDA-regulated articles such as dietary supplements, cosmetics, or foods.¹⁷ Subsequently, the FDA is unprepared to regulate a large class of potential products; application processes that adequately address the issues of safety for this group have yet to be characterized. This legal ambiguity discourages innovators by convoluting an already expensive evaluation process and limits the overall market accessibility of these products.

II. COMBINATION PRODUCTS LEGISLATION

Regulators of combination products must ensure that they are properly labelled and unadulterated before entering the market. Even then, however, the traditionally easy placement into one of six regulatory categories is insufficient. Instead, the FDA requires alternate legislation to determine whether combination products comply with safety law. According to the FFDCA, the regulation of combination products is based upon the determination of the primary mode of action (PMOA) for that product.¹⁸

16 21 U.S.C. § 353(g) (2013).

17 U.S. FOOD & DRUG ADMIN., *supra* note 9.

18 21 U.S.C. § 353(g).

According to the Code of Federal Regulations (CFR), a mode of action is defined as the means by which “a product achieves its intended therapeutic effect or action. For purposes of this definition, ‘therapeutic’ action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.”¹⁹ Combination products contain multiple regulated, constituent parts with distinct modes of action.²⁰ The PMOA is subsequently defined as the mode of action that provides the most important overall therapeutic effect. The PMOA is used to establish the agency center that will have primary jurisdiction over the regulation of the combination product.

For example, a drug-eluting stent (which is used to treat blocked or narrowed blood vessels) has two modes of action: (1) as a device, it provides a mechanical scaffold to keep a blood vessel open, and (2) as a drug, it prevents the buildup of new tissue within the artery. In this case, the product’s PMOA is the device’s function of physically maintaining the shape and functionality of the artery, whereas the drug plays a secondary role in reducing the reoccurrence of tissue buildup within the artery in response to the stent implantation. To an FDA regulator, the drug is viewed as simply augmenting the effectiveness of (and appendicular to) the initial stent-treatment. As a result, the CDRH would have primary jurisdiction in the regulation of a drug-eluting stent.²¹

In products where the modes have separate functions (neither of which are subordinate) and do not fit any discernable hierarchy of action, the agency will assign the product to the center that already regulates combination products that pose similar safety and effectiveness questions.²² If no substantially equivalent products exist, the agency assigns the product to the center with the most expertise in addressing the most significant safety questions presented

19 21 C.F.R. § 3.2(e) (2013).

20 42 U.S.C. § 351(i).

21 U.S. FOOD & DRUG ADMIN., *supra* note 8.

22 *Id.* at 49,850

by the combination product.²³ For example, a contact lens combined with a drug to treat glaucoma has two distinct, unrelated modes of action: (1) as a device that improves sight and (2) as a drug that treats glaucoma. Thus, a PMOA cannot be established. In addition, no combination product intended to treat these different conditions simultaneously (as a whole) has previously been submitted to any agency for review. Therefore, the product must be submitted to the agency with the most expertise in addressing the safety and effectiveness questions presented by the product. In this case, these relate to the drug component; safety questions raised by the contact lens are considered more routine.²⁴

As stated within FFDCA, “nothing . . . shall prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article.”²⁵ In other words, despite the fact a single agency may have primary jurisdiction over the regulation of a combination product, this does not preclude consultations by other agencies or the use of separate applications when evaluating a product.²⁶ The regulation of combination products is ultimately a collaborative effort by multiple authorities.

III. VACCINE FRUITS AS COMBINATION PRODUCTS

(i) Development of an Edible Vaccine

Hepatitis B (HB) is an infectious inflammatory illness of the liver caused by a virus. The disease is highly prolific; an estimated one-third of the world's population has been infected with the disease at some point in their lives. The Hepatitis B Vaccine (HBV) currently represents an effective, safe, and commercially successful form of immunization for the disease. However, a group of research-

23 *Id.* at 49,850.

24 *Id.* at 49,857.

25 21 U.S.C. § 353(e).

26 21 C.F.R. 3.4(b).

ers has sought to develop an equivalent vaccine that can serve third world countries, which remained burdened by HB epidemics due to the prohibitive cost of treatment.²⁷

The current form of HBV is classified as a subunit vaccine, which only contains the Hepatitis B surface antigen protein (which is sufficient to produce an effective immune response to the virus). A determining implication of the subunit vaccine is that the genes that encode for the vaccine antigen can be expressed by transgenic yeast cells or plant varieties.

Utilizing this feature, researchers sought to develop an oral version of HBV.²⁸ At present time, subunit vaccines are not yet cost-effective enough to be licensed for oral delivery.²⁹ Scientists investigated the use of an alternative vaccine delivery method by expressing the vaccine antigen protein within edible plants and feeding these plants as food to mice. These efforts were motivated by a desire to not only reduce vaccine production costs, but, because the vaccines are grown as food crop, countries would be able to support long-term product manufacture using indigenous agriculture and food processing technology. Researchers speculate that this could bolster the pharmaceutical autonomy of developing countries.

Test-trial results of the edible vaccine are compelling:

Oral immunogenicity of recombinant hepatitis B surface antigen (HBsAg) derived from yeast (purified product) or in transgenic potatoes (uncooked unprocessed sample) was compared... Transgenic plant material containing HBsAg was the superior means of both inducing a primary immune response and priming the mice to respond to a subsequent parenteral injection of HBsAg.³⁰

Since the paper describing this new HBV vaccine delivery system was published, numerous other inspired research groups have ex-

27 KONG ET AL., *ORAL IMMUNIZATION*, *supra* note 10, at 11539.

28 Oral vaccines (as opposed to parenteral or injectable vaccines) are safe, successful, alternative forms of vaccine delivery.

29 KONG ET AL., *ORAL IMMUNIZATION*, *supra* note 10, at 11539.

30 *Id.* at 11539.

perimented with oral, plant derived vaccines. Transgenic bananas and tomatoes (considered more palatable for human consumption), for example, are currently being evaluated in experiments similar to those described within the study but for a much wider range of affliction, including tuberculosis and measles.³¹

(ii) Edible Vaccines as Combination Products

Assuming these products are submitted for evaluation by the FDA, a regulatory pathway will need to be determined in order to ensure their safety. Genetically-modified, edible vaccines fit well within the algorithm used to assign primary jurisdiction to combination products.

In this case, the product has two modes of action. One action of the product is the action of the biological product component; this component stimulates the body's immune system to recognize and fight the Hepatitis B virus.³² The other action of the product is the food component's action to provide nourishment via naturally occurring proteins, carbohydrates, vitamins, and nutrients found within traditional, commercially available bananas. Here, both actions are independent and therefore neither appears to be subordinate to the other. Because it is not possible to determine which mode of action provides the greatest contribution to the overall therapeutic effects of the combination product, it is necessary to proceed along the assignment algorithm and determine whether or not there is a center within the FDA that regulates a product that poses similar questions of safety.

The CFSAN regulates bananas; the CBER regulates vaccine products. No combination product intended to both communicate viral resistance and to provide general nutrition as a food product has

31 *Id.* at 11544.

32 "A constituent part has a biological product mode of action if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings, as described in section 351(i) of the Public Health Service Act." 21 CFR § 3.2.

previously been reviewed by either agency. Though both the Center for Food Safety and Applied Nutrition and CBER regulate products that raise similar safety and effectiveness questions with regard to the constituent parts of the product, neither agency regulates combination products that present similar safety and effectiveness questions regarding the product as a whole. Therefore, it is necessary to apply the second regulatory criterion which determines the center with the most expertise in addressing the most significant safety and effectiveness questions presented by the product.³³

In this case, the banana (food) component presents generally routine safety and effectiveness questions, similar to those of other genetically modified food products. In contrast, the biological product component raises more significant safety and effectiveness questions, such as those related to antigen protein dose, sterility, purity, and potency. Based on this criterion, this product would be assigned to CBER because CBER has the most expertise related to these issues.

(iii) Regulation Alternatives Are Insufficient

Food and drug law investigators have explored a variety of ways to address the issue of banana vaccine regulation. In *Biopharming, Bananas and Bureaucracy*, author Margaux Birdsall, analyzes the differences between drug and food definitions, and she argues that the intent of a product's development is sufficient in directing the regulatory guidelines for edible vaccines.³⁴ Evaluation as a combination product, however, represents the only existing regulatory pathway for genetically modified, edible vaccines. In addition, their

33 U.S. FOOD & DRUG ADMIN., *supra* note 8.

34 Margaux Birdsall, *Biopharming, Bananas and Bureaucracy: The Banana Vaccine as a Case Study for Products that Straddle the Definitional Food/Drug Divide*, 66 FOOD DRUG L.J. 265, 265-82 (Jan. 2011). According to Birdsall's proposed reforms, "the manufacturer intent would guide the classification. If the manufacturer truly intended a new bioengineered product to primarily be a food, then it would be regulated as one. The same would apply to a manufacturer's intent to regulate a product as a drug."

physical characteristics disqualify them from other forms of regulation as either (1) a food product and food additive or (2) a pharmaceutical crop.

Food additives are defined as any material that may become a component of or otherwise modify the chemical composition of a food and that has not been generally recognized as safe (GRAS).³⁵ There are numerous examples of synthetic, manmade chemicals that have no GRAS, naturally augmented or isolated equivalent (examples include sodium and potassium nitrate, color additives, artificial sweeteners, etc.)³⁶ According to the FDA Guidance for New Plant Varieties, these chemicals “must be approved prior to its use by the issuance of a food additive regulation, based on information submitted to the FDA in a food additive petition”.³⁷ If the food additive is deemed safe or admissible based on the food additive petition (which includes quantification of identity, probable exposure, evaluation of safety, and conditions of use), the FDA then develops regulation specifying the conditions under which the additive may be safely used.³⁸

Food additives are combined with a food product in a controlled manner to ensure their concentration falls within allowable levels

35 21 U.S.C. § 321(s).

36 GRAS designations are awarded to foods or other substances that have either historically posed little to no risk to humans (in the case of a substance used in food prior to January 1, 1958) or there is a consensus among the evaluative scientific community that the substances demonstrate no probable threat. Examples include salt, sugar, monosodium glutamate, etc. 21 U.S.C. § 321(s).

37 Statement of Policy - Foods Derived from New Plant Varieties, 57 Fed. Reg. (May 29, 1992) *available at* <http://www.fda.gov/Food/Guidance-Regulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm>.

38 *Guidance for Industry: Questions and Answers About the Petition Process*, U.S. FOOD & DRUG ADMIN. (Apr., 2011), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm253328.htm>.

wherein the additive can be considered harmless.³⁹ In foods that have been genetically modified (GM) to express novel, unnaturally occurring chemicals (typically pesticide and herbicide proteins), the FDA ensures that these genetic modifications pose no threat to human safety. Specifically, GM foods are profiled with respect to whether or not they contain similar levels of risk universal to all foods, which is evaluated by analyzing relative allergen, toxin, and anti-nutrient content.⁴⁰ If the GM food product is determined as being substantially equivalent to its naturally occurring counterpart, genetically engineered foods and food byproducts are treated identically to foods developed by traditional plant breeding techniques and are considered GRAS.⁴¹

Unlike artificially combined food additives, genetically modified foods cannot generate chemicals that fail to satisfy GRAS designation requirements. Whereas traditional food additives can be added to foods in metered quantities so as not to exceed maximum allowable limits of intake, edible plants represent a virtually limitless range of shape and size variability. By extension, food additive content could potentially range considerably between one organism to the next, or could accumulate at varying concentrations within the tissue of the organism itself. Unless it can be reasonably established that a food additive concentration falls within experimentally determined levels of safety, or that such a designation is representative of all transgenic food items, the product is considered adulterated and

39 *Overview of Food Ingredients, Additives & Colors*, U.S. FOOD & DRUG ADMIN. (Apr., 2010), <http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm094211.htm>.

40 “Under section 402(a)(1) of the act, a food is deemed adulterated and thus unlawful if it bears or contains an added poisonous or deleterious substance that may render the food injurious to health or a naturally occurring substance that is ordinarily injurious.” Statement of Policy - Foods Derived from New Plant Varieties, 57 Fed. Reg. (May 29, 1992) *available at* <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocuments-RegulatoryInformation/Biotechnology/ucm096095.htm>.

41 U.S. GEN. ACCOUNTABILITY OFF., GENETICALLY MODIFIED FOODS: EXPERTS VIEW REGIMEN OF SAFETY TESTS AS ADEQUATE, BUT FDA’S EVALUATION COULD BE ENHANCED, 9–17 (May 2002).

misbranded and cannot be legally introduced into interstate commerce.⁴²

The antigen protein present within edible vaccines that are responsible for immunization against Hepatitis B represents a non-GRAS chemical. While subunit vaccines themselves are not considered particularly dangerous to human health, the fact that their concentrations are likely to fall either above or below their established dosages places them in violation of Title 21 Sec. 351(b), which states a product is adulterated if its strength, quality, or purity differs from official compendium.⁴³

Pharmaceutical crops, which are defined as plants that have been genetically engineered to produce non-food, non-feed, medical, or industrial products, avoid this violation because they are exclusively regulated as their isolated pharmaceutical or industrial compounds.⁴⁴ In other words, the final container of these products is not the plant itself. Instead, the commercial chemicals are purified from these crops and utilized as an isolate.⁴⁵ A vaccine compound that is grown using tobacco crop, isolated, and converted into an injectable vaccine that can subsequently be measured to conform to appropriate dosage standards satisfies all purity, potency, and sterility re-

42 21 U.S.C. § 342.

43 21 U.S.C. § 351(b).

44 Examples of species that have been used to produce pharmaceutical and industrial compounds to include: rice, corn, barley, tobacco, and safflower. These crops are grown to produce “research chemicals, vaccines, human antibodies, and human blood proteins.” Since 1991, nearly 200 applications to grow pharmaceutical and industrial crops in open fields have been granted. BRS Factsheet, Biotechnology Regulatory Services. (Feb., 2006).

45 Container (referred to also as “final container”) is “...the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange. A filling refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.” 21 U.S.C. § 321(l).

quirements for a biological product and is physically and chemically indistinguishable from traditionally fashioned vaccines.⁴⁶

(iv) Additional Regulatory Complexity

While both food and biologics regulations aim to minimize risk to human health, like other combination products, each promulgate and utilize substantially different definitions of the term “*safety*.” According to the CFR, agricultural products intended for human consumption may be recognized as safe with an understanding that food cannot represent anything that is poisonous or deleterious to human health.⁴⁷

As such, it is important to reiterate that GM foods are not regulated with the intent of ensuring absolute safety, but rather to demonstrate comparable safety to their non-GMO counterpart. As stated within a GAO Report to Congressional Requesters:

There is no assurance that even conventional foods are completely safe, since some people suffer from allergic reactions, and conventional foods can contain toxins and antinutrients. Because they have been consumed for many years, though, conventional foods are used as the standard for comparison in assessing the safety of GM foods, and experts note that the available tests are capable of making this comparison.⁴⁸

Unlike biologics, long-term testing and assessment of purity, sterility, dosage, etc. are not warranted by current manufacturing and evaluation laws of food crops. Scientists and food regulators alike acknowledge that an attempt to identify the long term effects of eating a food substance would be confounded by the great variability in eating patterns, food access, and way people react to foods. In addition, virtually all breeding techniques (both traditional and chemically manipulated) have the potential to create unintended effects

46 Permit User’s Guide with Special Guidance for ePermits, USDA-APHIS Biotechnology Regulatory Services, 16 (Mar. 7, 2012).

47 21 C.F.R. § 130.3.

48 U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 41, at 16.

that may or may not be deleterious, and subsequently any attempts at ensuring precise genetic homogeny of food crops are futile.

It is simply outside the scope of modern technology and statistical analysis to develop a long-term study about the potential effects of any foods. In addition, standardization and evaluation of every detail of food composition and effects would pose an insurmountable burden on the agricultural industry and its regulatory agencies. Although food is too complex to regulate with absolute certainty of safety, it is familiar and conventional enough to be classified as GRAS and regulated within reasonable safety guidelines. According to the FDA Guidance for food safety, plant breeders are recognized as having identified and eliminated plants that represent potential health risks and for using well-established practices to ensure their products' safety.⁴⁹ Thus, with respect to GM food products, "the best [and only] defense against long-term health risks from GM foods is an effective pre-market safety assessment process"⁵⁰ (by comparing them to their GRAS, traditionally bred counterparts).

While all substances may have some level of inherent risk, unlike foods, biologics are not designated as GRAS but do have a greater capacity to be subject to standardization and uniform production, and are subsequently held to a much higher standard of regulation.

For example, General Biological Products Standards provide that each lot must be tested for potency, general safety, sterility, purity, and identity.⁵¹ For the test sample itself to be deemed appropriate, an additional subset of factors must be taken under consideration, including the size and volume of the final product lot and the final container's size and configuration.⁵²

Even still, biologics are subject to an assessment of purity, which is defined, in part, as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or del-

49 U.S. FOOD AND DRUG ADMINISTRATION, *supra* note 37.

50 U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 41, at 32.

51 A lot is defined as "a quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel." 21 C.F.R. § 600.3(x).

52 *See Id.* § 610.12.

terious to the product.”⁵³ In other words, products are required to be free of all extraneous materials (even GRAS substances) except those which are unavoidable in the manufacturing process described in the approved biologics license application. In addition, biological products are expected to have the capacity to reliably produce a given therapeutic effect that is congruent with sufficient laboratory testing and clinical data.⁵⁴

The disparity between food and drugs is difficult to solve under current regulatory framework. While the combination product designation serves GM edible vaccines better than both *food additive* and *industrial crop* placement, this product still poses a unique challenge to agency components. In the past, many novel GMO products posed challenges to regulators and, as a result, guiding regulatory principles like *substantial equivalence* or *general recognition of safety* are used to simplify the safety assessment process and preserve the GMO industry as relatively innovation-friendly in nature.⁵⁵

Under biologics regulations for vaccines, however, products must effectively demonstrate potency, safety, purity, and identity to be considered free of adulteration. Organically grown edible plants are challenged to meet these stringent dosage-controlled constraints and are further burdened when ultimately deployed to in-country production. This presents a critical issue as, in many ways, GM vaccine fruits are only incentivized if they can be regulated as traditional banana crop. Evaluation of purity, sterility, and potency during the application process all increase the regulatory costs associated with a given product and limit its accessibility.

As such, new information and direction by the FDA is needed to classify GM vaccine fruits as safe. Specifically, in-depth risk assessment of these products is warranted to determine the relevance of current regulation. FDA officials will need to investigate edible vaccines’ product potential to meet adequate safety controls while being simultaneously subjected to less stringent regulation. Signifi-

53 See *Id.* § 600.3(r).

54 See *Id.* § 610.10.

55 Andrea Pirondini & Nelson Marmioli. *Environmental Risk Assessment in GMO Analysis*, 101 RIV. BIOLOGIA 215, 215-246 (2008).

cant safety and effectiveness questions would need to be addressed, including, at a minimum, those related to (1) comparative studies of oral vs. parenteral vaccinations, (2) an analysis of natural variation in banana crop populations, (3) enhanced subunit vaccine characterization, and (4) a re-evaluation of GRAS components and designations.

Subsequent findings and recommendations by regulatory officials may elicit several amendments to the FFDCa by Congress, including those that would expand the definition of a combination product to include food-drug and food-biologics combinations and necessitate the creation of additional, clarifying guidance for the regulation of these unique products.

IV. CONCLUSION

Since their inception, laws regulating combination products have been passed, often with great controversy, based on the latest developments in scientific understanding and opinion. The fact that combination products rest on the cutting edge of scientific discovery inevitably means their governing laws are constantly subject to change while requiring regulatory agencies to constantly monitor companies for infractions.

In addition, as transgenic research expands and the potential for additional forms of edible vaccines continues to grow, it will be important to monitor the relevance of current regulation and its applicability to meet adequate controls in this expanding market. Foods that are able to produce drug and biologic substances represent a quantum leap in products that are cheaper, safer, and more nutritionally enhanced. As combination products, GM food vaccines have the greatest potential to be accurately evaluated, although subsequent unprecedented questions of safety and effectiveness require further characterization of the product itself to be resolved.