PAST AND PRESENT U.S. PUBLIC HEALTH LAWS AND REGULATIONS, AND THEIR IMPACT ON THE CORRESPONDING FDA REGULATED PRODUCTS AND INDUSTRIES

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ABSTRACT

This white paper will address past and present U.S. public health laws and regulations and their impact on the corresponding FDA regulated products and industries. For almost a century, the U.S. FDA (Food and Drug Administration) has been a public health law enforcement agency regulating foods, cosmetics, human and animal drugs, biologics, tissues, medical devices, combination products, and tobacco products. As a response from various public health tragedies and the sale of deceptive products, the U.S. Congress has enacted various public health laws including the 1944 Public Health Service (PHS) Act, the 1906 Food and Drugs Act, and its successor – the 1938 Food, Drug, and Cosmetic (FD&C) Act. Today, there are over 200 U.S. public health and consumer protection laws and regulations, with the major quality and regulatory law being the 1938 U.S. FD&C Act. The 1938 FD&C Act is a U.S. law that grants the FDA the enforcement power to regulate various products including human and animal foods, drugs, biologics, tissues, cosmetics, medical devices, combination products, and tobacco products. Since 1938, there have been numerous revisions to the U.S. FD&C Act, including the Food and Drug Omnibus Reform Act of 2022 (FDORA), which further strengthened FDA's regulatory and inspectional authorities, while also allowing FDA to partner with regulated industries to develop better biologics, pharmaceuticals, and medical devices for distribution within the U.S. marketplace.

PAST AND PRESENT U.S. PUBLIC HEALTH LAWS AND REGULATIONS

To be regulated by the FDA (Food and Drug Administration), foods, cosmetics, human and animal drugs, biologics, tissues, medical devices, combination products, and tobacco products have to meet the federal public health definitions (such as noted in the Food, Drug, and Cosmetic (FD&C) Act and the Public Health Service (PHS) Act). Under the Food, Drug, and Cosmetic (FD&C) Act and the Public Health Service (PHS) Act, FDA (Food and Drug Administration) personnel has the authority to regulate products for medical purposes (such as drugs, biologics, tissues, medical devices, and combination products) through one of its three medical products centers, namely, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH), depending on the specific product type. If animal and clinical studies are required to justify the safety and effectiveness of drugs, biologics, tissues, medical devices, and combination products, industry personnel are also required to comply with the applicable FDA BIMO (bioresearch monitoring) requirements under 21 CFRs (code of federal regulations) 50-58. After the drug, biologic, tissue, medical device, and combination products have been approved, manufactured, and distributed, FDA requires the product owners, manufacturers and/or initial importers to report serious adverse events (such as deaths, reactions, and illnesses pertaining to drugs, biologics, and combination products approved by CBER and CDER, and deaths, serious injuries and malfunctions pertaining to medical devices and combination products approved by CDRH) and submit post-market surveillance to the FDA (i.e., for high-risk drugs, biologics, medical devices, and combination products). Various FDA databases [such as Risk Evaluation and Mitigation Strategies (REMS) and Manufacturer and User Facility Device Experience (MAUDE)] are used to monitor risk-benefit and adverse event data for pharmaceuticals, biologics, medical devices, and combination products. If high-risk public health events occur, the pharmaceutical, biologic, medical device, and combination product company personnel may conduct adverse products corrections, removals, or recalls or be forced to do so by the FDA. In certain cases, the FDA may also cause the company personnel to cease manufacture and/or distribution of affected products.

On the other hand, non-medical products, including foods, cosmetics, and tobacco products are also federally regulated. However, the majority of public health laws were surrounding the economics, quality, and safety of food products. Many of these public health laws resulted from public health tragedies and poor manufacturing practices.

Since the late 1700s, numerous U.S. federal laws and regulations addressed food safety, including (a) the 1789 Act for Laying a Duty on Goods, Wares and Merchandises Imported into the US; (b) the 1883 Impure Tea Act; (c) the 1906 Food and Drugs Act; and (d) the 1938 U.S. Food, Drug, and Cosmetic Act). During this time, there were also numerous public health tragedies and fraudulent economic acts that caused Congress to enact several public health laws, such as (a) illness and deaths from the poorly manufactured smallpox vaccines that enacted the 1813 Vaccine Act; (b) deaths from poorly made diphtheria antitoxins that

enacted the 1902 Biologics Act; (c) unsanitary Chicago meat packing operations that exacted the 1906 Food and Drugs Act); and (d) the deceptive sale of milk, butter, cheese, and beef products that enacted the 1987 Act for Protection of Dairymen and the 1923 Filled Milk Act. As a result of these public health tragedies and economic sales of unadulterated and misbranded products, food safety became the key responsibility of the U.S. Food and Drug Administration (formerly the Bureau of Chemistry from 1903-1930).

Before the creation of the FDA in 1930, Dr. Harvey Washington Wiley headed the Bureau of Chemistry under the Department of Agriculture, in which he hired volunteers known as the 'poison squad' to eat various foods as part of a dietary study of food preservatives. The performance of the 'poison squad' coupled with Upton Sinclair's book 'The Jungle' (which detailed the horrific conditions of the Chicago meat packing industry) caused the 1906 Food and Drugs Act to be enacted. The 1906 Food and Drugs Act (aka the Wiley Act) covered threats from harmful food and pharmaceutical substances and deceptive practices (such as fake patent medicines with secret and/or narcotic ingredients and/or misleading labels or oleomargarine labeled as butter). However, the Wiley Act failed to address the safety of cosmetics or medical devices.

Today, there are over 200 U.S. public health and consumer protection laws and regulations, with the major quality and regulatory law being the 1938 U.S. Food, Drug, and Cosmetic (FD&C) Act. The FD&C Act is a U.S. law enforced by the FDA that came about from the 1937 elixir of sulfanilamide pharmaceutical tragedy involving the death of over 100 infants and children. Since 1938, there have been numerous revisions to the U.S. FD&C Act (i.e., the replacement of the 1906 Foods and Drugs Act), including (a) October 18, 1968: Radiation Control for Health and Safety Act of 1968 (RCH&S); (b) October 10, 1962: Drug Efficacy Amendment; (c) May 28, 1976: Medical Device Amendments of 1976; (d) November 28, 1990: Safe Medical Device Act of 1990 (SMDA); (e) June 16, 1992: Medical Device Amendments of 1992; (f) April 1996: FDA Export Reform and Enhancement Act of 1996; (g) November 21, 1997: FDA Modernization Act of 1997 (FDAMA); (h) October 26, 2002: The Medical Device User Fee and Modernization Act of 2002 (MDUFMA); (i) September 27, 2007: FDA Amendments Act of 2007; (j) 2012: Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA); (k) 21st Century Cures Act of 2016; (l) FDA Reauthorization Act of 2017 (FDARA); (m) The Modernization of Cosmetics Regulation Act of 2022 (MOCRA); and (n) the Food and Drug Omnibus Reform Act of 2022 (FDORA).

Just like the 1938 FD&C Act, many of these FD&C Act revisions resulted from additional public health tragedies, such as (a) the pharmaceutical thalidomide tragedy in the 1960s which caused major birth defects in Europe; and (b) the 1989 Chilean Grape crisis in which FDA inspectors found 2 grapes poisoned with cyanide from a Chilean fruit shipment. Nevertheless, the updated FD&C Act gave FDA additional power over the various FDA-regulated products (such as the collection of user fees and increased food, drug, and medical device inspections). With the passing of the Act and corresponding amendments, Congress forced the FDA to develop and enforce various current good manufacturing practices (GMPs) under Title 21 code of federal regulation (CFR) for foods, drugs, biologics, tissues, medical devices, and combination products. As such, the following industries are currently impacted under the FDA Good Manufacturing Practices (GMP) regulations: (a) Combination Products Industry (21 CFR Parts 3, 4); (b) Automated systems Industry (21 CFR Part 11); (c) Food Industry (21 CFR Parts 106, 110, 111, 112, 113, 114, 117); (d) Pharmaceuticals Industry (21 CFR Parts 210, 211, 212, 312); (e) Medical Devices Industry (21 CFR Parts 803, 806, 807, 809, 812, 814, 820, 821, 822, and 830); (f) Biotech, Blood, and Tissue Industries (21 CFR Parts 606, 1270, and 1271), and Animal Drug and Feed Industry (21 CFR Parts 225, 226, 507, 510, 511). However, there currently exists no GMP regulations for the FDA regulated cosmetic and tobacco product industries.

Besides the FD&C Act, the FDA also enforces numerous amendments (such as the 1954 Miller Pesticide Amendment and the 1958 Food Additives Amendment, in which various food standards have been established) and portions of other public health laws, including (a) Northern Border Counternarcotics Strategy Act of 2010 (111-356); (b) Food Safety Law (111-353); (c) Secure and Responsible Drug Disposal Act of 2010 (111-273); (d) Combat Methamphetamine Enhancement Act of 2010 (111-268); (e) Intelligence Authorization Act for Fiscal Year 2010 (111-259); (f) Fair Sentencing Act of 2010 (111-220); (g) Indian Arts and Crafts Amendments Act of 2010 (111-211); (g) Patient Protection and Affordable Care Act (111-148); (h) Federal Anti-Tampering Act (Oct. 13, 1983); (i) Sanitary Food Transportation Act (Nov. 3, 1990); (j) Mammography Quality Standards Act (MQSA) (Oct. 27, 1992); (k) Bioterrorism Act of 2002 (June 12, 2002); and (l) Project BioShield Act of 2004 (July 21,

2004). With these various laws and regulations, the FDA is able to protect U.S. public health. Sanctions for adulterated and misbranded FDA-regulated products include product seizures and detentions, site injunctions, and industry prosecutions. In some cases, FDA works with state and local health agencies to embargo unsafe food products.

Even though no GMP regulations currently exist for the cosmetic and tobacco product industries, cosmetics (except for non-medicated soap products) and tobacco products are also regulated by the FDA. Initially, tobacco products were considered as FDA regulated pharmaceuticals, medical devices, or combination products. However, the safety and efficacy requirements for pharmaceuticals, medical devices, and combination products would deem all tobacco products as unadulterated and misbranded products. Thus, these products would no longer be allowed to be sold through interstate commerce within the United States. After many lengthy and numerous court battles through state and federal courts (such as FDA v. Brown & Williamson Tobacco Company, 529 U.S. 120, 2000), tobacco products are no longer considered as FDA regulated pharmaceuticals, combination products, or medical device products. However, the question still remained as to which federal agency would regulate tobacco products. With the 2009 enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA), it was determined that the FDA would regulate tobacco products.

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) (H.R. 1108, S. 625) was enacted in 2009 by U.S. Congress to: (a) require all tobacco product manufacturers to register annually with the FDA and provide the agency with a detailed product list; (b) mandate biennial inspection of all registered establishments; (c) require premarket approval of new tobacco products unless they were determined to be substantially equivalent to other tobacco products already on the market; (d) require manufacturers to obtain FDA approval in order to make reduced risk and reduced-exposure claims for their products, including the use of descriptors such as "light," "mild," and "low"; (e) authorize FDA to regulate the advertising and promotion of tobacco products in order to protect public health; (f) give FDA the authority to modify the composition of tobacco products in order to protect public health (though it would prohibit FDA from eliminating nicotine or banning tobacco products); (g) require FDA to develop new regulations for the testing, reporting, and public disclosure of tobacco product ingredients and smoke constituents; (h) preserve the authority of states and localities to take additional measures to restrict the distribution, advertising, promotion, sale, access to, and use of tobacco products; (i) instruct FDA to issue new recordkeeping requirements to help counter the illicit trade of tobacco products; and (j) assess user fees on manufacturers to pay for the cost of FDA tobacco regulation. Under FSPTCA, a tobacco product is now defined as: "(1) The term 'tobacco product' means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). (2) The term 'tobacco product' does not mean an article that is a drug under [21 U.S.C. § 321](g)(1), a device under [21 U.S.C. § 321](h), or a combination product described in [21 U.S.C. § 353](g). (3) The products described in paragraph (2) shall be subject to chapter V of this Act" [Food, Drug, and Cosmetic Act] (FDCA). Additionally, the FSPTCA defines modified risk tobacco product as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease.

Just like tobacco products, there are no GMP regulations currently in place for the manufacture of cosmetics products. Currently, it is FDA's responsibility to prove that cosmetic products are adulterated and misbranded through product testing. However, with the enactment of the 2022 Consolidated Appropriations Act, which also contained the Food and Drug Omnibus Reform Act of 2022 (FDORA) and The Modernization of Cosmetics Regulation Act of 2022 (MOCRA), the U.S. Congress gave the FDA an additional regulatory framework pertaining to biological products, cosmetics, drugs, and medical devices.

OVERVIEW OF THE FD&C ACT

As a result of the 1937 elixir of sulfanilamide pharmaceutical tragedy involving the death of over 100 infants and children, the U.S. Congress enacted the 1938 Food, Drug, and Cosmetic (FD&C) Act. Initially, the FD&C Act addressed the economic, quality, and safety issues for foods, biologics, and drugs while also giving the FDA the enforcement power over additional products such as cosmetics and medical devices. However, it was the FDA and not industry who had to prove through product testing that any interstate foods, cosmetics, drugs, biologics, and medical devices were truly unadulterated and misbranded.

Over the years, the 1938 FD&C Act has been amended to give FDA more enforcement power over these and other products (such as combination products, tissue products, and tobacco products). Additionally, the amendments to the FD&C Act also forced the FDA to develop current good manufacturing practices (cGMPs) for foods, drugs, biologics, tissues, medical devices, and combination products. Because no cGMPs currently exist for cosmetics and tobacco products, FDA still has to prove that these products have been adulterated and misbranded by the regulated industries. Since no enforceable cGMPs currently exist for cosmetics and tobacco products, it has been industry practice for over 50 years to self-regulate while utilizing various industry standards. For example, ISO 22716 (Cosmetics – Good Manufacturing Practices (GMP) – Guidelines on Good Manufacturing Practices) addresses the GMPs for cosmetics. For tobacco products, there are over 60 ISO standards currently in place.

OVERVIEW OF THE FOOD AND DRUG OMNIBUS REFORM ACT OF 2022 (FDORA)

With the passing of the FD&C Act and corresponding amendments, Congress forced the FDA to develop and enforce various current GMPs under Title 21 code of federal regulation (CFR) for foods, drugs, biologics, tissues, medical devices, and combination products. As such, the following industries are currently impacted under the FDA Good Manufacturing Practices (GMP) regulations: (a) Combination Products Industry (21 CFR Parts 3, 4); (b) Automated systems Industry (21 CFR Part 11); (c) Food Industry (21 CFR Parts 106, 110, 111, 112, 113, 114, 117); (d) Pharmaceuticals Industry (21 CFR Parts 210, 211, 212, 312); (e) Medical Devices Industry (21 CFR Parts 803, 806, 807, 809, 812, 814, 820, 821, 822, and 830); (f) Biotech, Blood, and Tissue Industries (21 CFR Parts 606, 1270, and 1271); and Animal Drug and Feed Industry (21 CFR Parts 225, 226, 507, 510, 511). However, there currently exists no GMP regulations for the FDA regulated cosmetic and tobacco product industries.

Even though the 1938 FD&C Act defined cosmetic products (with the exemption of non-medicated soap) and the enforcement of unadulterated and misbranded cosmetics, it is FDA's current responsibility to prove that cosmetic products are adulterated and misbranded through product testing. Since the U.S. Congress has not forced the FDA to develop GMPs for cosmetics for over 50 years, the cosmetic industry has been self-regulated. The same is true for the tobacco industry – a self-policing industry. However, for over a decade, cosmetic stakeholders have asked the FDA to modernize the cosmetic regulations, which have not significantly changed since the implementation of the 1938 FD&C Act. No such request has come from the tobacco industry to date.

With the enactment of the 2022 Consolidated Appropriations Act, which also contained the Food and Drug Omnibus Reform Act of 2022 (FDORA), the U.S. Congress gave the FDA an additional regulatory framework pertaining to biological products, cosmetics, drugs, and medical devices. With the passing of the Food and Drug Omnibus Reform Act of 2022 (FDORA), both the 1944 Public Health Service (PHS) Act and the 1938 Food, Drug, and Cosmetic (FD&C) Act will be amended. The FDORA includes 6 subtitles pertaining to reauthorizations, drugs and biologics, medical devices, infant formulas, cosmetics, and cross-cutting provisions. Even though the FDORA has not specifically addressed new enforcement actions by the FDA, this new amendment to the FD&C Act will definitely have short- and long-term effects on both the FDA and the regulated industry, such as:

The reauthorization of the following nine existing FDA programs through fiscal year 2027:

- Critical path public-private partnership
- The best pharmaceuticals for children program
- The humanitarian device exemption incentive
- The pediatric device consortia program
- The provision pertaining to drugs containing single enantiomers
- Certain device inspections
- Orphan drug grants
- Reporting requirements related to pending generic drug applications and priority review applications, and
- The third-party review program.
- Requiring biologic application holders to promptly report the marketing status of their biologic products
- The creation of national centers of excellence

in advanced and continuous pharmaceutical manufacturing by the FDA

- The banning of medical devices for one of more intended uses
- The protection of infants and improving formula supply
- The modernization of the cosmetic regulations
- The improvement of FDA device, bioresearch monitoring (BIMO, and foreign inspections, and
- Diversity plans for clinical studies.

The majority of the FDORA reauthorized the clinical, quality, and regulatory approval aspects for biological products, drugs, and medical devices, including:

- A public-private partnership that fosters medical product innovation, accelerates medical product development, manufacturing, and translational therapeutics, and enhances medical product safety
- Incentives to create better pediatric pharmaceuticals while also promoting pediatric device development
- The requirement of drug and device post-approval studies
- The development and implementation of diversity action plans for certain drug and device clinical trial studies
- The reporting on the review of biologic and pharmaceutical rare disease submissions
- The improvement of the humanitarian device exemption (HDE) requirements
- The implementation of an emerging technology program that supports innovative approaches to pharmaceutical design and manufacturing
- The elimination of animal testing for new drug and biosimilar marketing applications
- The expedition for the development and review of drug and biologic NDAs (new drug applications) and BLAs (biologic license applications)
- Requiring medical device developers and manufacturers of cyber devices to address, identify, monitor, and plan cybersecurity vulnerabilities of the marketed devices, and
- The allowance of medical device manufacturers voluntarily requesting a GMP inspection by an accredited third party instead of the FDA.

Besides the 2022 Act reauthorizing various clinical, quality, and regulatory approval aspects for biological products, drugs, and medical devices, it also allows FDA to:

- Perform unannounced foreign inspections, and
- Require cosmetic manufacturers to register their establishments and list their products, report adverse events to the FDA, and to comply with GMPs under the Modernization of Cosmetics Regulation Act of 2022 (MOCRA).

Just like the other amendments to the 1938 FD&C Act, the Food and Drug Omnibus Reform Act of 2022 (FDORA) further strengthened FDA's regulatory and inspectional authorities. Additionally, FDORA will also allow FDA to partner with regulated industry to develop better biologics, pharmaceuticals, and medical devices for distribution within the U.S. marketplace. However, the true test of FDORA will be FDA's implementation and enforcement of new regulations (such as registration, listing, and GMP requirements for cosmetic companies) and how the regulated industries react to these upcoming regulations.

Even though there are exciting and challenging times as a result of the enactment of the 2022 FDORA, EVERSANA's Global Quality Solutions will lead the way against the FDORA and upcoming FDA regulations. Our team will strategically work with you to develop a plan for successful regulatory compliance and continuous improvement by managing, performing, and/or accessing your quality management system (QMS) through document creation and/or revision, first-, second-, and third-party audits and gap assessments, FDA 483 and Warning Letter reconciliations, and other quality assurance and regulatory compliance activities and tasks. Learn more: https://www.eversana.com/solutions/integrated-commercial-services/integrated-compliance/quality-assurance-quality-management-systems/

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