ANALYSIS OF VARIABILITY IN REGULATORY REQUIREMENTS FOR PRODUCT APPROVAL, MANUFACTURING, AND POST-MARKET SURVEILLANCE OF HUMAN AND VETERINARY MEDICAL DEVICES IN THE UNITED STATES

by

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(Under the Direction of David Mullis)

ABSTRACT

Clear differences in the way FDA regulates human and veterinary medical devices were noticed by the researcher during tenure as a Quality Assurance professional in the animal health industry. This prompted research which examined the differences in regulation of human and veterinary medical device pre-market clearance, manufacturing control, and post-market surveillance through the review of data describing the development of federal laws, authorized agencies, and regulatory methodologies applied to device regulation. The research methodology included the evaluation of identifiable gaps in regulation and qualitatively assessed risk to veterinary medical device safety and effectiveness relative to identifiable gaps. Multiple gaps were identified and the magnitude of risk to veterinary medical device safety and effectiveness, and impact to human safety, was established.

INDEX WORDS: Human, Veterinary, Drug, Device, Biologic, Approval, Manufacturing, Manufacturing Control, Post-market Surveillance, Regulation, FDA, USDA, Risk-based.

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DEDICATION

This thesis is dedicated to Regulatory Affairs and Quality Assurance professionals in the human and veterinary pharmaceutical and biologics industries worldwide, who must read, understand, and apply volumes of regulation and guidance in order to ensure compliance with regulation, drug safety, drug potency and protection of human and animal health in the development, manufacture, and distribution of drugs, devices, and biologics.

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CHAPTER 1

INTRODUCTION

Regulatory requirements for product approval, manufacturing, and post-market surveillance of human and veterinary medical devices vary significantly in the United States (US). Initially, it is striking that products which seem so inherently similar, and in fact in some cases are identical, would be subject to different approval pathways, manufacturing controls, and post-market surveillance requirements. However, the dissimilarities of these medical devices and their target species may have necessitated these differences in regulation. Understanding these dissimilarities, as well as how specific regulatory agencies historically evolved, supports the degree to which these regulations vary and prompts questions concerning the appropriateness of regulatory variability, inherent risks, resource usage, and compliance monitoring relative to veterinary medical devices. Although veterinary and human medical devices are both regulated by the US Food and Drug Administration (FDA), and both are expected to be safe and effective, there is considerably less regulation for veterinary medical device pre-market clearance, manufacturing control and post-market surveillance, which potentially puts both animal and human health at risk by permitting potentially unsafe devices to be marketed without FDA review. FDA's current approach to regulation of veterinary medical devices is insufficient to ensure that veterinary medical devices are safe and effective.

Specific questions considered in this research include the following:

1. Why are firms which market veterinary medical devices not required to follow the Pre-market Approval (PMA) process under section 515 of the Federal Food, Drug, and Cosmetic Act?[1]
2. Why are firms which market veterinary medical devices not required to follow the Pre-market Notification (510k) process under Title 21 of the US Code of Federal Regulations (CFR) Part 807?[2]
3. Why are firms which exclusively manufacture veterinary medical devices not subject to specific Quality Systems Regulation specified in Title 21 CFR Part 820 when these regulations define clear systems required to support safety and effectiveness in control of the design, manufacture, and distribution of medical devices?[3]
4. Why are firms which exclusively manufacture veterinary medical devices not subject to pre-market inspection by the US FDA when some could potentially be lacking the basic quality systems and controls to ensure that veterinary medical devices are safe and effective?
5. Why are firms which market veterinary medical devices not subject to post-market surveillance reporting requirements in Title 21 CFR Part 822 which would require firms to develop a plan to monitor and report adverse experiences which could identify safety concerns with their device?[3,4]

Answers to these questions will be found in a qualitative comparison of the current regulation, as well as a review of the historical development of the FDA and its Centers. An assessment of this review will indicate that science- and risk-based methodologies should be applied to veterinary medical devices for more consistent regulation and management of approval, manufacturing control, and post-market surveillance in order to protect companion animal (i.e. pets) and production animal (i.e. food or food-producing animal) health and safety, which can have a direct impact on human health.[5]

Purpose of the Research

Establishing the same regulatory requirements for both human and veterinary medical devices at first may appear preferable in order to gain efficiency in government and industry, to reduce cost and risk, and to harmonize the systems, methodologies and approaches to quality management of medical devices. However, as indicated in the hypothesis described in Chapter 3, a risk assessment of the qualitative evaluation of regulations and the evolution of various regulating agencies, and careful consideration of the various target species, support the approach that science- and risk-based methodologies should be applied to all classes of medical devices for all target species, human or animal, for more consistent regulation and management of approval, manufacturing control, and post-market surveillance.

Detailed records exist which identify legally marketed human medical devices, but there is no comparable data identifying the number of veterinary medical devices marketed in the US. FDA's PMA database contains twenty-four

thousand four hundred thirty-eight (24,438) unique PMA numbers,[6] and FDA's 510(k) database contains one hundred thirty-three thousand seven hundred seven (133,707) releasable 510(k)s[7] (which include devices which have been demonstrated to be substantially equivalent to devices already legally marketed in the US, and excludes certain Class I and Class II devices which are exempt from pre-market notification).[8] It is unknown how many veterinary medical devices are marketed in the US since there is not a requirement for pre-market approval, pre-market notification, or post-market surveillance reporting, although FDA is aware of such medical devices through market surveillance, review of labeling when voluntarily submitted by the manufacturer, and review of voluntarily reported adverse events and product defects, and does regulate them.[9] The absence of specific applied regulation allows the introduction of risk in the use of veterinary medical devices for animal health and current FDA requirements for veterinary medical device label review are insufficient to prevent human and animal safety issues. Such medical devices include injectors for sterile injectable products, applicator guns for topical solutions, oral bolus applicators, transdermal injectors, and dental applications. Many companion animal and production animal vaccination and parasiticide programs utilize some of these veterinary medical devices to protect animal and human health. Veterinary hospitals and veterinary clinics use many of the medical devices developed for surgery and diagnosis or prevention of disease in humans, or similar devices uniquely developed for animals, such as catheters, pacemakers, hip and other joint prostheses, scalpels, and surgical gloves. The current approach to regulation of

these veterinary medical devices is therefore insufficient to ensure animal safety and device effectiveness.

Research to support the hypothesis includes a qualitative review of applicable regulation and agency guidance, including memoranda, notices, and public statements made by current and former FDA professionals, and the summary and assessment of experience the researcher has personally gained from more than fourteen (14) years of work in regulated industry (both human and veterinary pharmaceuticals and nutraceuticals, and veterinary biologics and medical devices), as well as comprehensive coursework in the University of Georgia College of Pharmacy's Graduate Program in Pharmaceutical and Biomedical Regulatory Affairs.

Outcomes of the Research

A comparison of the applicable regulations for pre-market clearance, manufacturing control and post-market surveillance of human and veterinary medical devices in the US will identify gaps in regulation of veterinary medical devices as well as resulting risk to animal and human health. Specific examples of risk associated with limited regulation of veterinary medical devices will be assessed in a risk assessment exercise and discussed to support the hypothesis. These examples will be expressed with specific human and veterinary medical devices currently marketed in the US.

Specific deliverables resulting from this research will include: (1) a clear qualitative comparison of the present variability in application of regulatory requirements for product approval, manufacturing, and post-market surveillance

of human and veterinary medical devices in the US presented in narrative and supplemented with tabular presentations of specific regulatory variability; (2) an assessment of risk associated with limited regulation of veterinary medical devices; and (3) research findings, conclusions and recommendations for industry and government.

CHAPTER 2

REVIEW OF THE LITERATURE: HISTORY OF MODERN REGULATION

Applicable laws, regulations, guidelines, and available agency and industry literature for human and veterinary drugs, medical devices, and biologics were reviewed in order to qualitatively assess differences. Organizational and legal history of drug and medical device regulation were reviewed in order to demonstrate why various agencies and their centers have responsibility of oversight for human and veterinary drugs, medical devices, and biologics. Warning letters and agency perspectives on human and veterinary medical device regulation were also reviewed in order to demonstrate how veterinary medical devices have been regulated. This information was accessed from the FDA web pages and databases referenced throughout this document and identified in the References section at the end of this document. Literature review was limited to this information because no other research regarding regulation of veterinary medical devices was discovered.

Laws and the Agencies They Shaped

Drug and medical device regulation today is the result of a culmination of experiences including deaths and serious adverse drug events and device experience over the last century. Even today these adverse experiences are shaping drug and device regulation and guidance worldwide. In the US, the evolution of FDA's current thinking is captured in reference to today's Good

Manufacturing Practice (GMP) regulation as “cGMP:”, where the “c” stands for “current”. cGMP is not only expressed as a regulatory requirement for the manufacture of drugs, but is also represented in the Quality System Regulation (QSR) for human medical devices. Statutory requirements in the Federal Food, Drug and Cosmetic Act or regulation in Title 21 of the US Code of Federal Regulations may be revised to support cGMP or may remain unchanged for several decades. FDA establishes how it applies cGMPs via Establishment Inspection Reports, Warning Letters, and Guidance Documents. FDA’s various Centers responsible for the review of human and veterinary drugs and devices [the Center for Drug Evaluation and Research (CDER), the Center for Biologic Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Veterinary Medicine (CVM)] have evolved over time out of necessity, and FDA is not the only US agency regulating human and veterinary drugs. The USDA’s Center for Veterinary Biologics regulates vaccines and biologic therapeutics for use in animals, and the US Environmental Protection Agency (EPA) regulates environmental impact of human and veterinary drugs and biologics. The historical development of each of these agencies resulted from specific needs over time, and each have an impact on current veterinary medical device regulation. Understanding how specific regulatory agencies historically evolved supports the degree to which current human and veterinary medical device regulations vary.

Human Drugs

In 1862, the USDA's newly formed Department of Chemistry was responsible for evaluating commodities such as fertilizer, but this department would in 1901 become the Bureau of Chemistry lead by Dr. Harvey Wiley whose function as a visionary for a science-based program of food and drug regulations would serve as the predecessor for the FDA.[10] Wiley's initial focus was on adulteration of food and he became known for his "Poison Squad", a group of men whose jobs were to consume food with known quantities of adulterants in order to study the effects on their health.[11] At the same time, uncontrolled patent medicines were being promoted as remedies for various illnesses and maladies and were actually killing adults and children since many contained toxic ingredients or had no affect on the illness being treated.[12] Drug manufacturers were known to dilute the strength of products in order to make them more profitable and consumers had no way of knowing whether drugs were safe or effective.[11] Wiley eventually rallied support for a law which would prevent the adulteration of food and drugs, and the Pure Food and Drugs Act was introduced in Congress.[11]

By 1906, a specific chain of events lead to the passage of the Pure Food and Drugs Act, when for the previous twenty-seven (27) years, almost one hundred (100) "bills had been introduced in Congress to regulate food and drugs" without much success[13]:

1. As previously mentioned, public support for regulation had grown as a result of Wiley's outcries of food and drug adulteration;

2. Upton Sinclair's *The Jungle* was published on 26 February 1906. The author intended to expose the horrible conditions under which laborers worked in the meatpacking industry, but the public was "most outraged at the disgusting filth and garbage in American food that this novel revealed"[14]; and
3. President McKinley had been assassinated in 1901 and was succeeded by his then-Vice President Theodore Roosevelt. President Roosevelt was "a man of rich knowledge" who pressed Congress to act in many areas, and has been considered one of the first politicians to "act responsibly in view of the changing economics and class structure of late-nineteenth-century America."[15] Upon the publication of *The Jungle*, Roosevelt was outraged and "demanded an official investigation."[14]

On 30 June 1906, the original Pure Food and Drugs Act was passed by Congress and signed into law by President Roosevelt. The Act prohibited "interstate commerce [of] misbranded and adulterated foods, drinks and drugs."[16]

The 1906 Act placed responsibility on the seller to ensure that drugs were unadulterated.[17]

> The basis of the law rested on the regulation of product labeling rather than pre-market approval. Drugs, defined in accordance with the standards of strength, quality, and purity in the United States Pharmacopoeia and the National Formulary, could not be sold in any other condition unless the specific variations from the applicable standards were plainly stated on the label.[13]

The 1906 Act provided for a regulatory function in addition to the Bureau of Chemistry's scientific mission.[11] However, the Act did not prohibit drug manufacturers from making false therapeutic claims and only prevented manufacturers from making "false and misleading statements about the ingredients or identity of a drug."[16] This was later remedied in 1912 in the Shirley Amendment, which prohibited making false therapeutic claims on drug labeling.[16]

Very little changed in terms of human drug regulation over the next ten (10) years, but reorganization within the government would lead to the creation of an organization named FDA. In 1927 the USDA's Bureau of Chemistry was split into two (2) separate agencies: the Food, Drug, and Insecticide Administration, which maintained responsibility for regulatory functions; and the Bureau of Chemistry and Soils, which maintained responsibility for research.[16] Then, in 1930, the Food, Drug, and Insecticide Administration was renamed the Food and Drug Administration after Congress removed funding for the regulation of pesticides.[16,17]

During the 1930's, it was becoming clear to the public and the government that the original 1906 Pure Food and Drugs Act was becoming obsolete and that a new law was needed to further protect consumers from drug adulteration and misbranding.[18,19] In 1933, FDA recommended a revision to the 1906 Act, and one was introduced in Congress, but a debate ensued which lasted five (5) years.[19] In the meantime, consumers were being seriously injured or killed by dangerous adulterated or misbranded drugs such as eyelash dyes, poisonous tonics, and false cures for diseases.[18] Finally, in 1937 the infamous Elixir of Sulfanilamide

tragedy occurred, where more than one hundred (100) people, including many children, were killed by an analog of antifreeze (diethylene glycol) that was used as a solvent for sulfanilamide, which was a recent medical advance that could kill a variety of infectious agents.[19] In response, the congressional debate ended, Congress passed The Federal Food, Drug, and Cosmetic (FD&C) Act of 1938, and President Franklin Roosevelt signed the Act into law.[16,19]

The 1938 FD&C Act introduced sweeping change in regulatory authority over human drugs. Specific changes resulting from the 1938 Act included the following:

- Medical devices and cosmetics were subject to regulation;
- Food packaging laws were more strict;
- Food standards were enforceable;
- Adulteration and misbranding were prohibited;
- Deceptive labels and containers were forbidden;
- New drugs had to be tested before going to market;
- Inspections of manufacturing facilities were authorized; and
- "The Shirley Amendment requirement to prove intent to defraud was removed."[16,19]

Other substantive changes that occurred after the introduction of the 1938 Act included the transfer of FDA from the USDA to the Federal Security Agency in 1940, the 1943 Supreme Court ruling in U.S. v. Dotterweich that corporations and their officials may be prosecuted for violations whether they were aware of them or not, the publication of FDA's first guidance document in 1949 entitled

“Procedures for the appraisal of the toxicity of chemicals in foods”, a 1950 court of appeals decision that drug labeling must include the purpose of the drug, and the 1951 Durham-Humphrey Amendment which defined which kinds of drugs must be made available by prescription only.[16,17] Then, in 1953, the Federal Security Agency became the Department of Health, Education, and Welfare.[17] The 1938 FD&C Act and subsequent amendments and court decisions had shaped the FDA into what we recognize today, but the agency and the law would continue to change.

In 1959, Senator Estes Kafauver lead an investigation into price-fixing, marketing, and side-effects of pharmaceuticals, which included over-promotion, safety, and false advertising.[17] Shortly thereafter, in 1962, it was discovered that a new sleeping pill marketed in Europe had caused severe birth defects in thousands of infants.[19] FDA had managed to keep the drug off the market in the US, but the alarm prompted even more rigorous regulation.[19] President John F. Kennedy appealed to Congress in 1962 that “legislation is needed to require drug manufacturers to maintain facilities and controls that will assure the reliability of their product.”[20] The Kefauver-Harris Amendments were passed that same year, strengthening the drug approval process by introducing the New Drug Application (NDA) process, requiring manufacturers to prove drug effectiveness before drugs could be marketed, defining adulterated drugs and GMP regulation, and requiring firms to report adverse events.[12,19,20]

The new law mandated efficacy as well as safety before a drug could be marketed, required FDA to assess the efficacy of all drugs introduced

since 1938, instituted stricter agency control over drug trials (including a requirement that patients involved must give their informed consent), transferred from the Federal Trade Commission to the FDA regulation of prescription drug advertising, established good manufacturing practices by the drug industry, and granted the FDA greater powers to access company production and control records to verify those practices.[21]

With the application of GMP defined in the law, improvements were seen in quality, safety, and efficacy of human drugs over the next several years and FDA continued to grow. FDA gained and lost some responsibilities in the 1960s and 1970s by being placed in the Public Health Service in 1968, incorporating the Bureau of Radiological Health in 1971 and the Bureau of Biologics Standards in 1972, and in 1984, the agency's Bureaus became Centers: the Center for Food Safety and Applied Nutrition, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Veterinary Medicine (CVM).[17,22] The Office of Regulatory Affairs (ORA) was assigned the responsibility of running the field force and laboratories around the country, and the National Center for Toxicological Research was assigned the responsibility of running toxicological testing.[17] Many changes continued within the agency, and many significant changes to administrative rules, patent terms, user fees, accelerated review, orphan drug approval, generic drug approval, and availability of investigational drugs were made to shape FDA into the organization we know today, but the foundation of human drug approval, manufacturing controls, and

post-market surveillance regulations had been established through tragedy, compromise, diligence, and commitment.[16,19,22] Today, FDA's CDER has responsibility for approval and post-market surveillance of human drugs while FDA's ORA is responsible for inspections and enforcement policy.

Human Biologics

As previously discussed, significant tragedy and considerable introduction of and changes to law and agency organization led to what we know today as FDA and GMP relative to regulation of human pharmaceutical drugs. Most of what has been discussed has also had a direct impact on the regulation of human biologics because, by FDA&C Act definition, biologics are drugs.[23]

Although The Vaccine Act of 1813 "was the first federal law dealing with consumer protection and therapeutic substances", it was short-lived, and no other law would be introduced to regulate vaccines or serums until passage of the 1902 Biologics Control Act after several children who received a diphtheria antitoxin made in horses died from antitoxin contaminated with tetanus.[11,16,19] A similar event occurred where several children died from smallpox vaccine contaminated with tetanus.[24] The 1902 Act was "designed to ensure the purity, potency and safety of these and other biologic products."[19] It authorized the Hygienic Laboratory of the Public Health and Marine Hospital Service to issue regulations requiring manufacturers of vaccines, serums, and antitoxins to be annually licensed, receive inspections, and clearly label their product with its name and expiration date.[24] Four (4) years later, the 1906 Pure Food and Drugs Act was passed, but it excluded any reference to biological products.

The predecessors to CBER were contributing to the protection of consumers, and from 1930 through the next several decades, introduction of new regulation and new agency organizational changes further improved the safety and oversight of human biologics. In 1930, the Public Health and Marine Hospital Service's Hygienic Laboratory was renamed the National Institute of Health. In 1938, the FD&C Act was passed and it defined biologics as drugs, but despite its sweeping change in regulatory authority over human drugs, the Act "did not modify or supersede the provisions of the 1902 Biologics Control Act," so both were subsequently applied to the regulation of human biologics.[24] In the late 1930s and early 1940s, there were concerns over the safety and efficacy of several vaccines, including those for polio, pertussis, influenza, and yellow fever.[24] During this time, serious problems with safety (insufficiently inactivated polio vaccine and virally contaminated yellow fever vaccine) and efficacy (potency of pertussis and influenza vaccines) were discovered and studied.[24] The Public Health Service Act was passed in 1944 and "included regulation of biological products and control of communicable diseases.[16,24] In 1955, the National Institutes of Health (NIH), formerly the National Institute of Health, created the Division of Biologics Control as an independent entity.[16] Finally, in 1972, the regulation of biologics was transferred from NIH to FDA.[24]

As previously mentioned, CBER was established in 1984, and is presently responsible for the review, approval, and post-market surveillance of human biologics within their jurisdiction, which include allergenics, blood and blood products, cellular and gene therapy products, tissues and tissue products,

vaccines, and xenotransplantation, and are also responsible for lot release of influenza virus vaccines.[25,26] The Centers for Disease Control and Prevention (CDC) is also responsible for post-market vaccine surveillance under the National Childhood Vaccine Injury Act of 1986.[27] Since biologics are also drugs under the FD&C Act, CDER is responsible for the review, approval, and post-market surveillance of certain therapeutic and other human biologics, and as with other drugs, FDA's ORA is responsible for inspections and enforcement policy.[24]

Human Medical Devices

Rapid development of substantive human medical device regulation began later than development of human drug and biologic regulation and relatively recently human device regulation has become quite complex with very specific pre-clearance and pre-market notification pathways, device tracking and device monitoring requirements, and the added complication of combination products, likely as a result of advances in technology.[28,29] Human medical devices were not included in the scope of the 1906 Act, possibly because of their relative simplicity at the time.[28,30] Human medical devices were not subject to regulation by FDA until the 1938 FD&C Act was passed by Congress and signed into law, and then only "equated them to drugs for regulatory purposes" in order to establish their regulation without actually promulgating GMPs for medical devices or requiring pre-market approval, while the number of devices on the market only grew.[16,19,30] Prior to 1938, only fraudulent medical devices had been regulated by the 1872 Postal Fraud Statute under the authority of the US Post Office and Postmaster General.[28] In 1971, the Bureau of Radiological Health was

placed under FDA, while at the same time a study group lead by Dr. Theodore Cooper was developing recommendations on medical device regulation following a request by the Secretary of the Department of Health, Education, and Welfare.[17,28] Recommendations made by “the Cooper Committee“ included: use of a different regulatory approach; an inventory of devices in the market; adoption of a classification system scheme; and application of good manufacturing processes with concomitant enforcement, inspection and record keeping responsibilities.”[28] Congress debated these recommendations until 1976, when the Medical Device Amendments were passed and made part of the FD&C Act “to ensure safety and effectiveness of medical devices, including diagnostic products.”[16] Important components of the amendments included the requirement of manufacturers to register with FDA and follow quality control procedures and the requirements to notify FDA of a device prior to marketing it, either through Pre-market Notification [510(k)] or Pre-market Approval (PMA) pathways, depending on the establishment of substantial equivalence or the assigned device classification.[28] cGMP requirements for devices in Title 21 CFR Part 820 were authorized by the FD&C Act under section 520(f), and this regulation became effective on December 18, 1978.[31] In 1984, FDA created the Center for Device and Radiological Health (CDRH), which became responsible for regulation of human medical devices as well as radiation-emitting products.[17]

The 1976 Medical Device Amendments had not included robust post-market surveillance requirements and provided for only limited enforcement of the law.[28] The Safe Medical Devices Act was passed in 1990 and required

healthcare professionals to report to FDA “incidents that suggest that a medical device probably caused or contributed to the death, serious illness, or serious injury of a patient, and required manufacturers to implement post-market surveillance on permanently implanted devices and to track such devices and their human patients with such devices.”[16,28] The Act also gave FDA the authority to recall certain devices.[28] Under the 2002 Medical Device User Fee and Modernization Act and its 2005 amendment, user fees were enacted to ensure timely reviews of devices, provide resources for regulatory reform, and to ensure safe and effective human medical devices are manufactured and marketed.[29]

Despite the fact that CDRH regulates human medical devices through regulation, review, approval, and post-market surveillance, these devices are becoming more complex as technology becomes more complex and other FDA Centers may actually have jurisdiction over certain combination products. As with human drugs and biologics, FDA’s ORA is responsible for human medical device manufacturing facility inspections and enforcement policy.

Human Combination Products

Human combination products present complex issues and the area of combination products is “one of the most challenging areas in regulatory affairs.”[28,32] The Office of Combination Products (OCP) was formed within the FDA’s Office of the Commissioner, “as mandated under the Medical Device User Fee and Modernization Act of 2002, to oversee review of products that fall into multiple jurisdictions within FDA,” but there are no current regulations specifically for combination products, and there is not a designated Center within FDA with

jurisdiction over combination products as a class.[16,32] Since this research began, FDA published a final rule in the Federal Register (78 FR 4307) on 22 January 2013 “clarifying which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products” in Title 21 CFR Part 4, which goes into effect on 22 July 2013.[33] FDA also published a draft guidance document titled *Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA*.[34] The primary responsibility of OCP for now is to determine which FDA Center will have the responsibility for reviewing a combination product, which is determined by the combination product’s primary mode of action.[28] Subsequently, the primary mode of action determines which FDA Center has regulatory jurisdiction and which regulations apply to the combination product.

Veterinary Drugs

Like human pharmaceutical drugs, veterinary drugs have been subject to changing regulation over the last century. Veterinary drugs were included in the scope of the 1906 Food and Drugs Act, and were therefore subject to the same requirements as human drugs, but over the course of several decades reorganization of the agency would ultimately assign the responsibility of veterinary drug approval and post-market surveillance to FDA’s Center for Veterinary Medicine (CVM) rather than CDER.[30,35]

The regulation of veterinary drugs followed the same path as that of human drugs into the 1950s, initially being overseen by USDA’s Bureau of Chemistry, then the Food, Drug, and Insecticide Administration in 1927, and then

the Food & Drug Administration in 1930, all the while being subject to the same applicable laws, including those provisions introduced in the 1938 FD&C Act and the significant Kefauver-Harris Amendments of 1962.[11,16,17,19] But in 1953, when the Federal Security Agency became the Department of Health, Education, and Welfare, a Veterinary Medical branch was established under the Bureau of Medicine whose "main function was to determine the safety of animal drugs both for human and animal consumers of food derived from treated animals."[17,36] The Food Additives Amendment of 1958 introduced additional provisions to protect human health from food-producing animals, and by 1959 the Veterinary Medical Branch from the Bureau of Medicine had become its own division.[30,35] As the use of animal drugs had increased, the government responded by creating the Bureau of Veterinary Medicine in 1968 and today's Center for Veterinary Medicine (CVM) in 1984.[17,30,35]

As with human drug regulation, several significant laws were passed over the last three (3) decades impacting the regulation of veterinary drugs. In 1988, the Generic Animal Drug and Patent Term Restoration Act permitted expedited approval for firms to manufacture and market generic versions of approved veterinary drugs and extended patents for the drug innovators, as had previously been provided for human generic drugs in the 1984 Drug Price Competition and Patent Term Restoration Act.[16,37] The 1994 Animal Medical Drug Use Clarification Act, the 1996 Animal Drug Availability Act, and the 2004 Minor Use and Minor Species Act each contributed to the unique needs of veterinary health by providing for extra-label use of drugs in certain circumstances, flexibility in the

drug approval process, and availability of drugs for rare veterinary diseases and species (not very unlike the 1983 Orphan Drug Act for human drugs), respectively.[16,34] In 2003, the Animal Drug User Fee Act was passed, which permitted FDA to collect user fees for animal drug review, as had previously been provided for human drugs and devices through the 1992 Prescription Drug User Fee Act and the 2002 Medical Device User Fee and Modernization Act.[16,34]

Like human pharmaceutical drugs, veterinary drugs have been subject to changing regulation over the last century, and today CVM has responsibility for veterinary drug approval and post-market surveillance, while ORA is responsible for establishment inspections and enforcement policy.[24,30]

Veterinary Biologics

Established in 1862, the USDA created the Department of Chemistry, which was responsible for evaluating commodities and would eventually become what we know today as FDA, but it wouldn't be until 1883 when the agency would establish a Veterinary Division, which was USDA's first regulatory program.[10,38,39] The Division's "original function was to acquire and disseminate agricultural information."[39] In 1884, the Division became the Bureau of Animal Industry (BAI), created by Congress "to promote livestock disease research, enforce animal import regulations, and regulate the interstate movement of animals," as well as focus "attention on the need for controlling animal diseases."[38,39] In 1913, Congress passed the Virus-Serum-Toxin Act which "gave the Secretary of Agriculture authority to license and regulate the production and trade of veterinary biologics."[40] BAI functions were incorporated into USDA's

Agricultural Research Service in 1953, and very important animal welfare and care laws and programs were enacted in the late 1960s, but very little changed in terms of regulation of veterinary biologics or agency structure until 1971 when the animal and plant regulatory functions were separated from the Agricultural Research Service to become the Animal and Plant Health Services (APHS) and ultimately the Animal and Plant Health Inspection Service (APHIS) in 1972.[38]

The Food Security Act of 1985 amended the Virus-Serum-Toxin Act of 1913 to broaden the Secretary of Agriculture's "authority to issue regulations, enhancing the Secretary's enforcement powers, and allowing USDA-APHIS to regulate all movement of veterinary biological products within or imported into the United States."[40] That same year, the Secretary designated APHIS as "responsible for regulating biotechnology-derived products that affect animal and plant health".[39,40] Today, veterinary biologics are regulated by the USDA-APHIS Center for Veterinary Biologics (CVB), created in 1996 and responsible for biologic approval, post-market surveillance, and field surveillance, including establishment inspection.[38,39]

Veterinary Medical Devices

Veterinary medical devices are regulated by FDA, but their regulation and oversight are approached very differently from the other products discussed above. As stated previously, human medical devices were not included in the scope of the 1906 Food and Drug Act and were not subject to regulation by FDA until the 1938 FD&C Act was passed by Congress, and then only "equated them to drugs for regulatory purposes" without requiring pre-market approval.[16,19,30]

But the 1938 Act did include veterinary medical devices in its scope of authority, since the definition of a device includes those devices used in animals:

> (h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c) [21 USC §§ 331(i), 343(f), 352(c), 362(c)]) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--
>
> (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
>
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
>
> (3) intended to affect the structure or any function of the body of man or other animals, and
>
> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.[41]

However, specific regulation published in the Federal Register and ultimately implemented in Title 21 of the US Code of Federal Regulations (CFR) §800-898, defining specific requirements for pre-market notification and approval, manufacturing controls, and post-market surveillance apply only to human medical devices and not veterinary medical devices. Because veterinary medical

devices are within the scope of the FD&C Act, FDA "can take appropriate regulatory action if a veterinary device is misbranded, mislabeled, or adulterated" and does recommend "that manufacturers and/or distributors of veterinary medical devices request a review of their product labeling and promotional literature to ensure that it complies with labeling and regulations."[42,43] FDA also recommends that firms manufacturing veterinary medical devices use the Quality Systems Regulation and other regulation included in Title 21 CFR §800-898 as a guide in the manufacture and assembly of their devices.[42] In fact, FDA has performed inspections of manufacturers of veterinary medical devices and has issued warning letters for adulteration of medical devices according to "Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21 CFR Part 820."[44,45] Additionally, FDA has issued safety alerts for devices which have introduced risk to animal safety.[46] Today, CVM has responsibility for veterinary device regulation, and according to Marea Harmon, a Consumer Safety Officer with CVM (oral communication, March 2012), CVM and CDRH are currently evaluating how CVM specifically regulates veterinary medical devices.

Regulatory Methodologies:

Development and Application of the Code of Federal Regulations, Including cGMPs and QSRs

Human Medical Devices

Human medical devices are subject to specific controls and pre-market clearance pathways specified in the regulations of Title 21 CFR §800-898.[47] As previously discussed, these regulations came as a result of the 1976 Medical Device Amendments, the 1990 Safe Medical Devices Act, and the 2002 Medical Device User Fee and Modernization Act.[16,28,29] A summary of regulations applicable to human medical devices from Title 21 CFR Chapter 1 Subchapter H is provided in Table 2.1 (Summary of Regulations Applicable to Human Medical Devices).[48] [Excluded from the scope of this research are mammography standards, radiological health, tobacco products, and certain other acts administered by the FDA specified in Title 21 CFR Chapter 1, Subchapters I, J, K, and L, respectively].[48] A review and discussion of specific regulations within the scope of this research applicable to medical device pre-market clearance, manufacturing controls, and post-market surveillance follows.

Table 2.1. Summary of Regulations Applicable to Human Medical Devices.[48]

Part	Heading
800	General
801	Labeling
803	Medical Device Reporting
806	Medical Devices; Reports of Corrections and Removals
807	Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices
808	Exemptions from Federal Preemption of State and Local Medical Device Requirements
809	In Vitro Diagnostic Products for Human Use
810	Medical Device Recall Authority
812	Investigational Device Exemptions
813	[Reserved]
814	Pre-market Approval of Medical Devices
820	Quality System Regulation
821	Medical Device Tracking Requirements
822	Postmarket Surveillance
860	Medical Device Classification Procedures
861	Procedures for Performance Standards Development
862	Clinical Chemistry and Clinical Toxicology Devices
864	Hematology and Pathology Devices
866	Immunology and Microbiology Devices
868	Anesthesiology Devices
870	Cardiovascular Devices
872	Dental Devices
874	Ear, Nose, and Throat Devices
876	Gastroenterology-Urology Devices
878	General and Plastic Surgery Devices
880	General Hospital and Personal Use Devices
882	Neurological Devices
884	Obstetrical and Gynecological Devices
886	Ophthalmic Devices
888	Orthopedic Devices
890	Physical Medicine Devices
892	Radiology Devices
895	Banned Devices
898	Performance Standard for Electrode Lead Wires and Patient Cables

Several parts of Title 21 CFR Chapter 1 Subchapter H listed above apply to human medical device pre-market clearance, manufacturing controls, and post-market surveillance. These regulations identify specific requirements for the various classes of medical devices. The scope and applicability of these parts are reviewed and discussed below in respective order of application to the medical device lifecycle relative to this research, and include in order of application[49]:

- Part 860, Medical Device Classification Procedures
- Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]
- Part 814, Pre-market Approval of Medical Devices
- Part 812, Investigational Device Exemptions
- Part 820, Quality System Regulation
- Part 801, Labeling
- Part 803, Medical Device Reporting
- Part 821, Medical Device Tracking Requirements
- Part 822, Postmarket Surveillance

Medical device classification defined in Part 860 is the current methodology for determining the level of risk, intended use, and indications for use associated with a particular device and the level of controls required for pre-market clearance, manufacturing controls and post-market surveillance (i.e. general controls with or without exemption, or general controls and special

controls with or without exemptions, or general controls and pre-market approval, as specified in the FD&C Act).[50] Medical devices are classified into one (1) of three (3) categories:

- Class I medical devices are those which require only general controls in order to "provide reasonable assurance of the safety and effectiveness of the device", or are devices which are not life-supporting or -sustaining but important in preventing impairment of human health and do not present unreasonable risk of illness or injury, but for which sufficient evidence does not exist to support that general controls may be sufficient to assure safety and effectiveness.[51]
- Class II medical devices are those which require special controls in addition to general controls in order to "provide reasonable assurance of the safety and effectiveness" of the device, as deemed necessary by the Commissioner.[51] Specific special controls (and performance standards) are prescribed by the Commissioner for these devices when they are intended to support or sustain human life.[51] Special controls are intended to address safety and effectiveness of a device by following recommendations of FDA device-specific guidance documents or by some other means that the manufacturer determines provides equivalent assurances of safety and effectiveness.[52] An example of a special control for non-topical tissue adhesive is FDA's Class II Special Controls Guidance Document *Tissue Adhesive for the Topical Approximation of Skin*.[53] Special controls and performance

standards applicable to specific medical devices are identified in Title 21 CFR Parts 862 through 892.

- Class III medical devices are those which require pre-market approval because insufficient information exists to determine that general controls and special controls provide assurance of safety and effectiveness and the devices are life-supporting or -sustaining, or "for a use which is of substantial importance in preventing impairment of human health," or presents a potential unreasonable risk of illness or injury."[51] "PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s)."[54] The PMA will include scientific elements such as technical data, nonclinical study data and clinical data.[54]

Medical device classification determines whether or not a device will be exempt or subject to pre-market notification or pre-market approval, and will determine the level to which certain controls are applied to the manufacture, distribution, and post market surveillance of the device. That is, medical device classification will determine the applicability of the regulations reviewed in this research.

According to Part 807, any firm (owner or operator) "engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of a device intended for human use [including in vitro diagnostics] shall register and submit listing information for those devices in commercial distribution," excluding in part those firms "engaged in the recovery, screening, testing,

processing, storage, or distribution of human cells, tissues, and cellular and tissue-based products," manufacturers of device raw materials or components, manufacturers of veterinary medical devices, manufacturers of reagents or laboratory equipment not marketed for medical use, licensed practitioners and firms manufacturing devices for their own use, carriers (i.e. transporters) of devices, and persons who dispense a device to perform a service through the use of a regulated device.[55] Registration information required to be provided to the agency includes:

> The name and mailing address of the device establishment; the Web site address of the device establishment, if any; the name, address, phone number, fax number, and email address of the owner or operator; the name, address, phone number, fax number, and email address of the establishment's official correspondent; and all trade names used by the establishment.[55]

Part 807 also establishes the device listing information required to be provided to the agency, which includes establishment registration number, device product codes, device brand names, FDA pre-market submission number, or pre-market notification, and a list of each activity or process performed relative to the device at each establishment.[55]

Pre-market notification procedures, also known as "510(k)"s referring to the section of the FD&C Act which authorizes them, are also outlined in Part 807. Subpart E specifically defines when a pre-market notification submission is required, information required in a pre-market notification submission, format of

the submission, content and format of the 510(k) summary and statement, misbranding by reference to pre-market notification, and FDA action on a pre-market notification.[55] Pre-market notification is a more efficient pathway to marketing clearance for a device that does not require pre-market approval, but is at least as safe and effective, or substantially equivalent, to a legally marketed device.[56] In CDRH's 1998 publication *The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications*, it is stated that "All Class I devices are exempt from the requirements of pre-market notification unless the device is intended for a use that is of substantial importance in preventing impairment to human health or presents a potential unreasonable risk of illness or injury," so there are some Class I devices which are not exempt from pre-market notification.[57] FDA has also exempted certain Class II devices from pre-market notification.[51] A list of specific Class I and Class II devices exempt from pre-market notification were published by FDA in the Federal Register in 1998.[51] Certain "preamendments" Class III devices (those devices marketed prior to the passage of the 1976 Medical Device Amendments) for which the FDA has not yet called for pre-market notifications may also be subject to pre-market notification rather than pre-market approval.[51]

Pre-market approval of medical devices is a complex process defined by the regulations identified in Part 814 of Title 21 CFR.[58] "Transitional, preamendment, or not substantially equivalent postamendment Class III devices," and certain Class I and Class II devices described previously, require

pre-market approval.[57,58] Pre-market approval is based on FDA's determination that the pre-market approval submission "contains adequate scientific evidence that the device is safe and effective for its intended use," and is only applicable to human medical devices.[58] The subparts of Part 814 establish requirements for pre-market approval application (PMA), FDA action on a PMA, postapproval requirements, and humanitarian use devices.[59] Data requirements for a PMA are extensive and partially include the following:

- A summary of data and information in the PMA, including: indications for use; alternative practices and procedures; marketing history (foreign and domestic); summary of studies (nonclinical and clinical) and conclusions drawn from studies; a complete description of the device, its components, properties, methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and installation of the device, as applicable;
- Reference to any performance standards, including how the device meets or deviates from such standards;
- Detailed technical sections describing clinical and nonclinical laboratory studies including "microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate," as well as

    clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse

reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations;

- Samples of the device and its components (if requested);
- Copies of all proposed labeling; and
- An environmental assessment.[59]

An investigational device exemption (IDE) is required when firms wish to introduce a device into intrastate commerce in order to study a device which is in development and has not received pre-market clearance.[60] The purpose of Part 812 is "to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose."[60] An approved IDE exempts a device from requirements of the FD&C Act for misbranding, establishment registration, device listing, performance standards, pre-market approval, banned device regulation, records and reports, restricted device requirements, and good manufacturing practices, although very specific rules and exceptions apply.[60] The application for IDE must contain an investigational

plan and a report of prior investigations, and any changes to the plan or associated protocols must be reported to FDA within specific timelines and specifying details of the change(s).[60]

Part 820 of Title 21 CFR establishes Quality System Regulation (QSR) which specifies the current Good Manufacturing Practices for "methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use."[61] This regulation establishes requirements for Quality Systems, including specific management responsibility for quality policy, organization, resources, responsibility, management review, procedures, quality audits, and qualification and training of personnel.[61] But the details of this part further specify in-depth requirements for document controls (approval, reviews, and revision), purchasing controls (supplier evaluation and records), identification and traceability, production and process controls (process changes, environmental control, maintenance of buildings and equipment, and process validation), acceptance activities, control of nonconforming product, corrective and preventive actions, device labeling and packaging control, handling, storage, and distribution procedures and records, device master records, device history records, servicing records, and complaint files.[61]

Labeling requirements for human medical devices specified in Part 801 provide for general labeling provisions (for prescription devices) as well as provisions for over-the-counter (OTC) devices and specific devices and exemptions.[62] General labeling provisions require the name and place of

business of the manufacturer, packer, or distributor, intended use and directions for use, prominence of required label statements, and use of Spanish language on the label(s).[62] OTC labeling provisions specify requirements for the principal display panel (the part of the label most prominent in the device's marketable form), statement of identity, contents, and warning statements.[61] Examples of special requirements for specific devices include "labeling of articles intended for lay use in the repairing and/or refitting of dentures," "user labeling for menstrual tampons," and "user labeling for latex condoms."[61]

Parts 803 (Medical Device Reporting), 821 (Medical Device Tracking Requirements), and 822 (Postmarket Surveillance) are all separate parts, but cumulatively achieve shared goals, which are to ensure device safety and effectiveness and to protect public health relative to marketed devices.[63,64,65] Medical device reporting requirements apply to all devices and require that deaths and serious injuries which devices have caused, may have caused, or may have contributed to, are reported to the agency by device user facilities (such as hospitals and nursing homes), manufacturers, distributors, and importers, and requires the maintenance of adverse event files.[63] Medical device tracking requirements require tracking of Class I and Class II medical devices to ensure that they can be adequately traced to the end user for effective market notification, market correction, or recall.[64] Post-market surveillance requirements for Class II and Class III devices are intended to ensure that post-market surveillance data can reveal unexpected adverse events.[65]

Veterinary Medical Devices

As discussed previously, the FD&C Act includes veterinary medical devices within the scope of federal law, but Title 21 CFR parts applicable to medical devices do not entirely include veterinary medical devices within their scope. In fact, FDA makes the following statements on their website:

- "FDA has regulatory oversight over veterinary medical devices and can take appropriate regulatory action if a veterinary device is misbranded, mislabeled, or adulterated."[9]
- "FDA does not require submission of a 510(k) or formal pre-market approval for devices used in veterinary medicine. It is the responsibility of the manufacturer and/or distributor of these articles to assure that these animal devices are safe, effective, and properly labeled."[9]
- "Device manufacturers who exclusively manufacture, or distribute veterinary devices are not required to register their establishments and list veterinary devices."[9]
- Although the Quality Systems Regulations published in Title 21, Code of Federal Regulations (CFR), Part 820, apply to human devices only, FDA recommends that veterinary device manufacturers become familiar with these regulations and be guided by them in manufacturing/assembling their device articles.[9]

These statements indicate that there is an FDA expectation that veterinary medical device manufacturers should ensure that their devices are safe and effective, but there was very little evidence to demonstrate active enforcement of

this expectation in this research, despite the fact that animal health can have a direct impact on human health via food-producing animals. For example, veterinary medical devices are used to support production animal vaccination and parasiticide programs through topical application or injection. Non-integral metal syringe tips may remain in food animal tissue post-injection and subsequently contaminate food.[66] Non-sterile injectors are commonly used with sterile injectable products in the food animal industry and several such devices are on the market with no specific instruction for sterilization. Also, in vivo diagnostics used in production animals may present certain residues impacting consumable meat or milk safety, particularly if they were developed specifically for use in animals versus use in humans.

This research included a review of available veterinary medical device regulatory enforcement on FDA's website. The Warning Letter Search Tool, available in FDA's Electronic Reading Room on the FDA website, was used to perform a search for Warning Letters associated with the phrases "veterinary device" and "veterinary medical device".[67] Both searches returned the same eight (8) records of warning letters, all for firms which manufacture or market human and veterinary medical devices or veterinary drugs.[68,69,70,71,72,73,74,75] Each was the result of violations of human medical device regulation or drug regulation and not specifically the result of marketing or establishment inspection infractions regarding veterinary medical devices. [68-75] In fact, the Warning Letter issued to Engler Engineering Corporation, "a manufacturer and distributor of human and veterinary dental polishers/accessories, ultrasonic scalers/accessories, and

veterinary devices," for non-conformance with the QSR specified in Title 21 CFR Part 820 and pre-market notification specified in 872.4200 and 872.4850 for dental devices, indicated that the firm should either submit pre-market notifications for the devices or label them "for veterinary use only."[70] A search of FDA's CVM News & Events for the phrase "veterinary device" returned only one public warning statement about possible danger associated with the use of a veterinary medical device on FDA's CVM Updates web page.[46] While the findings of this research indicate that there is little evidence to support regulatory enforcement of veterinary devices, there is evidence that some firms and device users do report adverse events and product defects to FDA, because at least two hundred eighteen (218) individual reports of adverse event clinical signs or product defects for various devices and various animal species can be found in CVM's Cumulative Veterinary Adverse Drug Experience (ADE) Reports from 1987 to 28 February 2013.[76] It must be noted, however, that it is not possible to specify whether these AE clinical signs reported for veterinary devices were for devices alone or for devices used concomitantly with other drugs or devices. That is, a veterinary AE clinical sign could possibly have been the result of a concomitantly used drug or device. For human devices, reporting is required if a device may have caused death or serious injury.[77]

CHAPTER 3

RESEARCH METHODOLOGY

Hypothesis

Although human and veterinary medical devices are both regulated by the US FDA, and both are expected to be safe and effective, there is considerably less regulation for veterinary medical device approval, manufacturing control, and post-market surveillance, which potentially puts both animal health and human health at risk by permitting potentially unsafe veterinary medical devices to be marketed without FDA review. FDA's current approach to regulation of veterinary medical devices is insufficient to ensure that veterinary medical devices are safe and effective.

More clear and robust regulation of veterinary medical devices will put animal safety and veterinary device effectiveness at less risk. Applying identical regulations and requirements to all classes of veterinary devices may not be appropriate in consideration of differences among target species and risk to safety and effectiveness. Applying a risk-based approach to new or revised regulations for veterinary medical devices will result in less risk without applying unnecessary burden on industry or regulators.

Methodology

In order to identify and evaluate specific gaps in regulation between human and veterinary medical devices, the execution of this research employs the following chronological steps: establishment of the scope of the research; review of the literature (original archived data from multiple sources); identification of specific gaps in application of medical device regulation which have an impact on veterinary medical device safety and effectiveness; and evaluation of those gaps.

Establishment of the Scope of the Research

Specific differences between regulation of human medical devices and regulation of veterinary medical devices observed by the researcher through professional experience in the animal health field include requirements for pre-market clearance, manufacturing controls, and post-market surveillance. The research questions identified in Chapter 1, the hypothesis, and the scope of the research were results of these observations.

Review of the Literature

Review of original archived data from multiple sources constitutes review of the literature and describes the study. Review of regulatory literature relative to pre-market clearance, manufacturing controls (e.g. cGMP), and post-market surveillance of human and veterinary medical devices and the development/organization of FDA's Centers and their jurisdictions includes:

1. The Federal Food, Drug & Cosmetic Act and amendments;
2. The Safe Medical Devices Act;

3. The Medical Device User Fee and Modernization Act and amendments;
4. Federal regulations applicable to premarket clearance, manufacturing control, and post-market surveillance of human and veterinary medical devices, in order of application relative to the research;
    a. Title 21 CFR Part 860, Medical Device Classification Procedures
    b. Title 21 CFR Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]
    c. Title 21 CFR Part 814, Pre-market Approval of Medical Devices
    d. Title 21 CFR Part 812, Investigational Device Exemptions
    e. Title 21 CFR Part 820, Quality System Regulation
    f. Title 21 CFR Part 801, Labeling
    g. Title 21 CFR Part 803, Medical Device Reporting
    h. Part 821, Medical Device Tracking Requirements
    i. Part 822, Postmarket Surveillance
5. Practices in veterinary medicine;
    a. Committee on the National Needs for Research in Veterinary Science, National Research Council. *Critical Needs for Research in Veterinary Science*
    b. *The Merck Veterinary Manual*. 9th ed

6. Warning letters for veterinary medical devices;

   The Warning Letter Search Tool, available in FDA's Electronic Reading Room on the FDA website, is used to perform a search for Warning Letters associated with the phrases “veterinary device” and “veterinary medical device”.

7. Safety alerts for veterinary medical devices;

   The general search tool for FDA’s website is used to search for “animal device” and “veterinary device” and safety alerts are noted and reviewed.

8. Print and non-print accounts of FDA history;

   a. *FDA: A History* [DVD]. Compliance Media; 2008

   b. FDA website. About FDA: FDA’s Origin, FDA History

   c. *Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements*

<u>Identification of Specific Gaps in Application of Medical Device Regulation</u>

1. Federal regulations applicable to premarket clearance, manufacturing control, and post-market surveillance of human medical devices are laid out in tabular form according to device class. Each regulation is labeled as applying to human medical devices and/or veterinary devices and human medical device classes subject to each part are identified.

2. Specific identical or similar medical devices utilized in both human and veterinary medicine are selected based on the knowledge of the

researcher. The selection criteria are: the device must be a Class I, Class II, or Class III device or equivalent (for veterinary devices); the device must be used in both human and animal species; and the device used in each species can be identical or conceptually similar. Similar or identical medical devices known by the researcher to be used in both humans and animals are selected and stratified into each class until three (3) devices are selected from each class. The devices selected for this purpose are intraoral dental wax, surgical gloves, non-resorbable gauze for external use, tissue adhesive for topical use, non-electrically powered fluid injectors, piston syringes, implantable pacemaker pulse generators, hip joint metal constrained cemented or uncemented prostheses, and intraocular lenses.

3. Federal regulations applicable to premarket clearance, manufacturing control, and post-market surveillance of each class of human medical devices are laid out in tabular form according to human medical device class. Each regulation is labeled as applying to the human medical devices and/or veterinary devices selected.

Evaluation of Specific Gaps in Application of Medical Device Regulation

Applying a risk-based approach to ensure medical device safety and effectiveness is consistent with the 2002 FDA current Good Manufacturing Practice Initiative for human and animal drugs and biologics, which focuses on identifying and mitigating the greatest risks to public health in manufacturing.[16] A risk assessment is a natural component of a risk-based approach and is the first

step in identifying mitigating actions and prioritizing them. Risk assessments factor the severity and occurrence of possible harm in order to assign a pre-defined level of risk, which is associated with an action or response to mitigate the specific risk.

1. A qualitative risk assessment tool (i.e. risk assessment matrix) is used to factor risk severity and risk occurrence to obtain a qualitative risk magnitude of low, medium, or high.
2. Classifications for severity of risk associated with not applying human medical device regulation to veterinary medical device pre-market clearance, manufacturing controls, and post-market surveillance are defined as low (may not impact safety and effectiveness), medium (may impact safety and effectiveness), or high (will impact safety and effectiveness).
3. Adverse event and product defect complaints for specific identical or similar medical devices utilized in both human and veterinary medicine are identified using the search functions in the CVM ADE Comprehensive Clinical Detail Report Listing and FDA's Manufacturer and User Facility Device Experience (MAUDE) database, using the following search criteria for each selected device:
    - Intraoral Dental Wax – MAUDE simple search; search term "dental wax"; date range "All years";

- Surgical Gloves – MAUDE advanced search; Product Class "Device: [Surgeon's] Gloves"; Date Report Received by FDA "01/01/1990" to "01/31/2013";
- Nonresorbable Gauze for External Use – MAUDE advanced search; Product Class "Device: Gauze/Sponge, Nonresorbable For External Use"; Date Report Received by FDA "01/01/1990" to "01/31/2013";
- Tissue Adhesive for Topical Use – MAUDE advanced search; Product Class "Tissue Adhesive for the Topical Approximation of Skin"; Date Report Received by FDA "01/01/1990" to "01/31/2013";
- Non-electrically Powered Fluid Injectors – MAUDE simple search; search term "fluid injector"; date range "All years";
- Piston Syringes – MAUDE advanced search; Product Class "Device: Syringe, Piston"; Date Report Received by FDA "01/01/1990" to "01/31/2013";
- Implantable Pacemaker Pulse Generators – MAUDE advanced search; Product Class " Device: Implantable Pacemaker Pulse Generators"; Date Report Received by FDA "01/01/1990" to "01/31/2013";
- Hip Joint Metal Constrained Cemented or Uncemented Prostheses – MAUDE advanced search; Product Class "Prosthesis, Hip, Constrained, Metal"; Date Report Received by FDA "01/01/1990" to "01/31/2013"; and

- Intraocular Lenses – MAUDE advanced search; Product Class "Device: Intraocular lens"; Date Report Received by FDA "01/01/1990" to "01/31/2013".
- For veterinary device AEs and PDs, the search conducted in the CVM ADE Comprehensive Clinical Detail Report Listing is performed by navigating to the database on the FDA website, selecting "D-I - ADE Summaries (accessible version)" from the Cumulative Veterinary ADE Reports (with a default date range of 1987 to February 28, 2013, at the time of the research), and searching for the term "device". AE clinical signs and product defects for each type of selected device are noted.

4. Classifications for risk associated with occurrence of adverse events in humans and adverse event clinical signs in animals (or product defects for veterinary devices) reported temporal to the use of specific Class I, Class II, and Class III medical devices are defined as low (adverse events <u>are not</u> documented in specified FDA databases for humans <u>or</u> animals), medium (adverse events <u>are</u> documented in specified FDA databases for humans <u>or</u> animals), or high (adverse events <u>are</u> documented in specified FDA databases for humans <u>and</u> animals);
5. The risk assessment matrix factors risk severity and risk occurrence to obtain a qualitative risk magnitude of low, medium, or high for each specific device selected when specific human medical device regulation is not applied to veterinary medical devices.

6. Study findings, gap and risk assessment results are presented, and conclusions and recommendations are made.

CHAPTER 4

RESEARCH RESULTS

Data collected following the methodology described in the previous chapter are presented in Tables 4.1 through 4.24. Tables are presented in the order in which data was gathered, assessed, or derived. Tables 4.1 through 4.4 identify specific gaps relative to application of specific regulation to Class I, Class II and Class III human medical devices and corresponding veterinary medical devices selected. Table 4.5 presents the risk matrix model for determining magnitude of overall risk to safety and effectiveness of specified veterinary medical devices. Tables 4.6 through 4.8 identify the risk classifications assigned for severity for the specific devices selected. Tables 4.9 through 4.11 identify the number of documented reports of adverse event (AE) clinical signs and product defects (PDs) from CVM's Cumulative Veterinary Adverse Drug Experience (ADE) Reports database for veterinary medical devices, and AEs for humans from FDA's Manufacturer and User Facility Device Experience (MAUDE) database, for the specific devices selected. Tables 4.12 though 4.14 identify the risk classifications assigned for occurrence for the specific devices selected. Tables 4.15 through 4.23 express the calculated qualitative risk magnitude for each of the selected veterinary medical devices when specific human medical device regulation is not applied. Table 4.24 summarizes risk magnitude calculated for each device.

Gaps in application of regulation are identifiable in the exclusion of veterinary medical devices from the scope of human medical device regulation in Table 4.1 relative to pre-market clearance, manufacturing controls, and post-market surveillance. Applicability of regulation to human medical device class is incorporated into the risk assessment data when AE occurrence is factored into the matrices in Tables 4.9 through 4.11.

Table 4.1. Title 21 CFR Parts Applicable to Medical Device Pre-market Clearance, Manufacturing Controls, and Post-market Surveillance.

Title 21 CFR Part	Human Medical Devices are in Scope (Yes/No)	Veterinary Medical Devices are in Scope (Yes/No)	Device Class(es) – Human Only (I, II, III)
Part 860, Medical Device Classification Procedures	Yes[51]	No[51]	I, II, III[51]
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	Yes[55]	No[55]	I, II, III[†55]
Part 814, Pre-market Approval of Medical Devices	Yes[59]	No[59]	III[59]
Part 812, Investigational Device Exemptions	Yes[60]	No[60]	I, II, III[††60]
Part 820, Quality System Regulation	Yes[61]	No[61]	I, II, III[††61]
Part 801, Labeling	Yes[62]	No[62]	I, II, III[62]
Part 803, Medical Device Reporting	Yes[63]	No[63]	I, II, III[63]
Part 821, Medical Device Tracking Requirements	Yes[64]	No[64]	II, III[64]
Part 822, Postmarket Surveillance	Yes[65]	No[65]	II, III[65]

[†]Exempt devices and devices requiring PMA are not subject to 510(k) pre-market notification requirements.
[††]With certain exemptions.

Three specific identical or similar medical devices utilized in both human and veterinary medicine were randomly selected from each human medical device class following criteria established in the methodology. The devices selected for this purpose were intraoral dental wax, surgical gloves, non-resorbable gauze for external use, tissue adhesive for topical use, non-electrically powered fluid injectors, piston syringes, implantable pacemaker pulse generators, hip joint metal constrained cemented or uncemented prostheses, and intraocular lenses.

Table 4.2. Title 21 CFR Parts Applicable to Class I Human Medical Device Pre-market Clearance, Manufacturing Controls, and Post-market Surveillance for Intraoral Dental Wax, Surgical Gloves, and Non-resorbable Gauze.

Title 21 CFR Part	Applies to Class I Human Devices (Yes/No)	Applies to Equivalent Veterinary Devices (Yes/No)
Part 860, Medical Device Classification Procedures	Yes[51]	No[51]
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	Yes[†55]	No[55]
Part 814, Pre-market Approval of Medical Devices	No[59]	No[59]
Part 812, Investigational Device Exemptions	Yes[60]	No[60]
Part 820, Quality System Regulation	Yes[61]	No[61]
Part 801, Labeling	Yes[62]	No[62]
Part 803, Medical Device Reporting	Yes[63]	No[63]
Part 821, Medical Device Tracking Requirements	No[64]	No[64]
Part 822, Postmarket Surveillance	No[65]	No[65]

[†] With certain provisions for pre-market notification for dental wax and gauze.[78,79]

Table 4.3. Title 21 CFR Parts Applicable to Class II Human Medical Device Pre-market Clearance, Manufacturing Controls, and Post-market Surveillance for Tissue Adhesive, Nonelectrically Powered Fluid Injectors, and Piston Syringes.

Title 21 CFR Part	Applies to Class II Human Devices (Yes/No)	Applies to Equivalent Veterinary Devices (Yes/No)
Part 860, Medical Device Classification Procedures	Yes[51]	No[51]
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	Yes[55]	No[55]
Part 814, Pre-market Approval of Medical Devices	No[†59]	No[59]
Part 812, Investigational Device Exemptions	Yes[60]	No[60]
Part 820, Quality System Regulation	Yes[61]	No[61]
Part 801, Labeling	Yes[62]	No[62]
Part 803, Medical Device Reporting	Yes[63]	No[63]
Part 821, Medical Device Tracking Requirements	Yes[64]	No[64]
Part 822, Postmarket Surveillance	Yes[65]	No[65]

[†]Tissue adhesive for non-topical use is a Class III device and requires a PMA.[80]

Table 4.4. Title 21 CFR Parts Applicable to Class III Human Medical Device Pre-market Clearance, Manufacturing Controls, and Post-market Surveillance for Implantable Pacemaker Pulse Generators, Hip Joint Metal Constrained Cemented or Uncemented Prostheses, and Intraocular Lenses.

Title 21 CFR Part	Applies to Class II Human Devices (Yes/No)	Applies to Equivalent Veterinary Devices (Yes/No)
Part 860, Medical Device Classification Procedures	Yes[51]	No[51]
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	Yes[55]	No[55]
Part 814, Pre-market Approval of Medical Devices	Yes[†59]	No[59]
Part 812, Investigational Device Exemptions	Yes[60]	No[60]
Part 820, Quality System Regulation	Yes[61]	No[61]
Part 801, Labeling	Yes[62]	No[62]
Part 803, Medical Device Reporting	Yes[63]	No[63]
Part 821, Medical Device Tracking Requirements	Yes[64]	No[64]
Part 822, Postmarket Surveillance	Yes[65]	No[65]

[†]With certain provisions for hip prostheses.[81]

A standard qualitative risk matrix was modeled after one used commonly in pharmaceutical, financial, and safety industries in order to factor risk severity and risk occurrence to obtain an overall risk magnitude of low, medium, or high for each selected device when specific human medical device regulation is not applied to veterinary medical devices.[82,83]

Table 4.5. Risk Matrix Model for Determining Magnitude of Overall Risk to Safety and Effectiveness of Specified Veterinary Medical Devices.

		Occurrence		
		Low	Medium	High
Severity	High	Medium	High	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium

Classifications for severity of risk associated with not applying human medical device regulation to veterinary medical device pre-market clearance, manufacturing controls, and post-market surveillance were defined as low (may not impact safety and effectiveness), medium (may impact safety and effectiveness), or high (will impact safety and effectiveness). Because Title 21 CFR Subparts applicable to pre-market clearance, manufacturing controls, and post-market surveillance are intended to ensure device safety and effectiveness, a critical assumption in severity risk classification in Tables 4.6 through 4.8 was that not applying these regulations to veterinary medical devices will always result in a high potential to impact safety and effectiveness.

Table 4.6. Severity Risk Classification for Class I Human Medical Device Regulation not Required to be Applied to Similar or Identical Veterinary Medical Devices (Intraoral Dental Wax, Surgical Gloves, and Non-resorbable Gauze).

Title 21 CFR Part	Severity
Part 860, Medical Device Classification Procedures	High
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	High
Part 812, Investigational Device Exemptions	High
Part 820, Quality System Regulation	High
Part 801, Labeling	High
Part 803, Medical Device Reporting	High

Table 4.7. Severity Risk Classification for Class II Human Medical Device Regulation not Required to be Applied to Similar or Identical Veterinary Medical Devices (Tissue Adhesive, Nonelectrically Powered Fluid Injectors, and Piston Syringes).

Title 21 CFR Part	Severity
Part 860, Medical Device Classification Procedures	High
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	High
Part 812, Investigational Device Exemptions	High
Part 820, Quality System Regulation	High
Part 801, Labeling	High
Part 803, Medical Device Reporting	High
Part 821, Medical Device Tracking Requirements	High
Part 822, Postmarket Surveillance	High

Table 4.8. Severity Risk Classification for Class III Human Medical Device Regulation not Required to be Applied to Similar or Identical Veterinary Medical Devices (Implantable Pacemaker Pulse Generators, Hip Joint Metal Constrained Cemented or Uncemented Prostheses, and Intraocular Lenses).

Title 21 CFR Part	Severity
Part 860, Medical Device Classification Procedures	High
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [and Pre-market Notification]	High
Part 814, Pre-market Approval of Medical Devices	High
Part 812, Investigational Device Exemptions	High
Part 820, Quality System Regulation	High
Part 801, Labeling	High
Part 803, Medical Device Reporting	High
Part 821, Medical Device Tracking Requirements	High
Part 822, Postmarket Surveillance	High

In order to define risk classifications for occurrence for the qualitative risk assessment, AE and PD data for specific medical devices utilized in both human and veterinary medicine were identified following the research methodology. This data is presented in Tables 4.9 through 4.11.

Table 4.9. AE and PD Reports for Veterinary Medical Devices and AE Reports for Human Medical Devices (Intraoral Dental Wax, Surgical Gloves, and Non-resorbable Gauze).

Device	Number of Human Device AE Reports	Number of Veterinary Device AE and PD Reports
Intraoral Dental Wax	0[84]	0[76]
Surgical Gloves	377[85]	0[76]
Non-resorbable Gauze for External Use	83[86]	0[76]

Table 4.10. AE and PD Reports for Veterinary Medical Devices and AE Reports for Human Medical Devices (Tissue Adhesive, Non-electrically Powered Fluid Injectors, and Piston Syringes).

Device	Number of Human Device AE Reports	Number of Veterinary Device AE and PD Reports
Tissue Adhesive for Topical Use	721[87]	5[76]
Non-electrically Powered Fluid Injectors	0[88]	35[†76]
Piston Syringes	500[89††]	35[†76]

[†]CVM ADE reports do not differentiate between non-electrically powered fluid injectors and piston syringes. All AE clinical signs and product defects for "syringes and needles" were included in each of these results. It has been established that AE and PD reports for non-electrically powered fluid injectors are included in these results.[46]

[††]Note that the MAUDE database search tool can in most cases only return a maximum of five hundred (500) results. This number may not represent every human device AE reported in the time period for piston syringes.

Table 4.11. AE and PD Reports for Veterinary Medical Devices and AE Reports for Human Medical Devices (Implantable Pacemaker Pulse Generators, Hip Joint Metal Constrained Cemented or Uncemented Prostheses, and Intraocular Lenses).

Device	Number of Human Device AE Reports	Number of Veterinary Device AE and PD Reports
Pacemakers	500[†90]	5[††76]
Hip Prostheses	3[91]	0[76]
Intraocular Lenses	500[†††92]	0[76]

[†] Note that the MAUDE database search tool can in most cases only return a maximum of five hundred (500) results. This number may not represent every human device AE reported in the time period for implantable pacemaker pulse generators.

[††]CVM ADE reports do not differentiate between pacemakers or defibrillators (internal or external). Therefore all AEs and PDs for "Pacemakers and Defibrillators" are included in this total.

[†††]Note that the MAUDE database search tool can in most cases only return a maximum of five hundred (500) results. This number may not represent every human device AE reported in the time period for intraocular lenses.

Occurrence of adverse events temporal to the use of selected human or veterinary medical devices was defined as the existence of documented

evidence in the FDA databases (CVM ADE Comprehensive Clinical Detail Report Listing and MAUDE) that an AE or AE clinical sign or quality defect had been reported to FDA.[76,84-92] Classifications for occurrence of risk associated with not applying human medical device regulation to veterinary medical device pre-market clearance, manufacturing controls, and post-market surveillance were defined as low (adverse events are not documented in FDA databases for humans or animals), medium (adverse events are documented in FDA databases for humans or animals), or high (adverse events are documented in FDA databases for humans and animals). See Tables 4.12 through 4.14.

Table 4.12. Occurrence Risk Classification for Class I Human Medical Device and Corresponding Veterinary Medical Device Adverse Events and Product Defects (Intraoral Dental Wax, Surgical Gloves, and Non-resorbable Gauze).

Device	Occurrence
Intraoral Dental Wax	Low
Surgical Gloves	Medium
Non-resorbable Gauze for External Use	Medium

Table 4.13. Occurrence Risk Classification for Class II Human Medical Device and Corresponding Veterinary Medical Device Adverse Events and Product Defects (Tissue Adhesive, Nonelectrically Powered Fluid Injectors, and Piston Syringes).

Device	Occurrence
Tissue Adhesive for Topical Use	High
Non-electrically Powered Fluid Injectors	Medium
Piston Syringes	High

Table 4.14. Occurrence Risk Classification for Class III Human Medical Device and Corresponding Veterinary Medical Device Adverse Events and Product Defects (Implantable Pacemaker Pulse Generators, Hip Joint Metal Constrained Cemented or Uncemented Prostheses, and Intraocular Lenses).

Device	Occurrence
Implantable Pacemaker Pulse Generators	High
Hip Joint Metal Constrained Cemented or Uncemented Prostheses	Medium
Intraocular Lenses	High

Severity and occurrence risk classifications were applied to the risk matrix model shown in Table 4.5 for each of the nine (9) selected devices. The classification for severity and occurrence were each identified from Tables 4.6 through 4.8 and 4.12 through 4.14, and the tabular cell at the intersection of the severity row and occurrence column in Tables 4.15 through 4.23 identify overall risk magnitude. Table 4.24 summarizes the overall risk magnitude determined for each device when specific parts of human medical device regulation are not applied to veterinary medical devices.

Table 4.15. Risk Matrix for Determining Magnitude of Overall Risk to Intraoral Dental Wax Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	Medium	High
Severity	**High**	**Medium**[†]	High	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium

[†]Severity is high, occurrence is low, and therefore risk magnitude is medium.

Table 4.16. Risk Matrix for Determining Magnitude of Overall Risk to Surgical Gloves Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	**Medium**	High
Severity	**High**	Medium	**High**[†]	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium

[†]Severity is high, occurrence is medium, and therefore risk magnitude is high.

Table 4.17. Risk Matrix for Determining Magnitude of Overall Risk to Non-resorbable Gauze for External Use Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	**Medium**	High
Severity	**High**	Medium	**High**[†]	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium

[†]Severity is high, occurrence is medium, and therefore risk magnitude is high.

Table 4.18. Risk Matrix for Determining Magnitude of Overall Risk to Tissue Adhesive for Topical Use Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	Medium	**High**
Severity	**High**	Medium	High	**High**[†]
	Medium	Low	Medium	High
	Low	Low	Low	Medium

[†]Severity is high, occurrence is high, and therefore risk magnitude is high.

Table 4.19. Risk Matrix for Determining Magnitude of Overall Risk to Non-electrically Powered Fluid Injectors Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	**Medium**	High
Severity	**High**	Medium	**High**†	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium

†Severity is high, occurrence is medium, and therefore risk magnitude is high.

Table 4.20. Risk Matrix for Determining Magnitude of Overall Risk to Piston Syringes Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	Medium	**High**
Severity	**High**	Medium	High	**High**†
	Medium	Low	Medium	High
	Low	Low	Low	Medium

†Severity is high, occurrence is high, and therefore risk magnitude is high.

Table 4.21. Risk Matrix for Determining Magnitude of Overall Risk to Implantable Pacemaker Pulse Generators Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	Medium	**High**
Severity	**High**	Medium	High	**High**†
	Medium	Low	Medium	High
	Low	Low	Low	Medium

†Severity is high, occurrence is high, and therefore risk magnitude is high.

Table 4.22. Risk Matrix for Determining Magnitude of Overall Risk to Hip Joint Metal Constrained Cemented or Uncemented Prostheses Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	**Medium**	High
Severity	**High**	Medium	**High**[†]	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium

[†]Severity is high, occurrence is medium, and therefore risk magnitude is high.

Table 4.23. Risk Matrix for Determining Magnitude of Overall Risk to Intraocular Lenses Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

		Occurrence		
		Low	Medium	**High**
Severity	**High**	Medium	High	**High**[†]
	Medium	Low	Medium	High
	Low	Low	Low	Medium

[†]Severity is high, occurrence is high, and therefore risk magnitude is high.

Table 4.24. Magnitude of Overall Risk to Assessed Veterinary Medical Device Safety and Effectiveness when Specific Parts of Human Medical Device Regulation are not Applied.

Veterinary Medical Device	Device Class for Corresponding Human Medical Device	Magnitude of Risk
Intraoral Dental Wax	Class I	Medium
Surgical Gloves		High
Non-resorbable Gauze for External Use		High
Tissue Adhesive for Topical Use	Class II	High
Non-electrically Powered Fluid Injectors		High
Piston Syringes		High
Implantable Pacemaker Pulse Generators	Class III	High
Hip Joint Metal Constrained Cemented or Uncemented Prostheses		High
Intraocular Lenses		High

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

Findings

As discussed in the previous chapters, Title 21 CFR parts applicable to medical devices do not entirely include veterinary medical devices within their scope which, according to the hypothesis, potentially puts both animal health and human health at risk by permitting potentially unsafe veterinary medical devices to be marketed without FDA review. Applicable laws, regulations, guidelines, and available agency and industry literature for human and veterinary drugs, medical devices, and biologics were reviewed in order to qualitatively assess differences. Organizational and legal history of drug and medical device regulation were reviewed in order to demonstrate why various agencies and their centers have responsibility of oversight for human and veterinary drugs, biologics, and particularly human and veterinary medical devices. A comparison of the regulation applicable to pre-market clearance, manufacturing controls, and post-market surveillance of human and veterinary medical devices identified gaps in the specific regulation of veterinary medical devices. Additionally, medical devices from each of the three (3) human medical device classes (i.e. Class I, Class II, and Class III), which are identical or similar to those used in veterinary medicine, were identified. These devices for both human and veterinary applications were divided by class assignment and assessed for application of

medical device regulations. A risk assessment was performed on each of the nine (9) medical devices examined in this research, which include intraoral dental wax, surgical gloves, non-resorbable gauze for external use, tissue adhesive for topical use, non-electrically powered fluid injectors, piston syringes, implantable pacemaker pulse generators, hip joint metal constrained cemented or uncemented prostheses, and intraocular lenses. The risk assessment considered severity and occurrence as factors in establishing the overall risk magnitude associated with impact to veterinary medical device safety and effectiveness when specific parts of human medical device regulation are not applied.

Relevant findings from this research include the following:

1. Veterinary medical devices are defined in the FD&C Act as medical devices and are therefore subject to regulation by FDA.[41]
2. Human medical devices are under the regulatory jurisdiction of CDRH, as well as other Centers depending on the device's primary mode of action.[17,28]
3. Human medical devices are classified into one (1) of three (3) categories: Class I (requiring only general controls in order to "provide reasonable assurance of the safety and effectiveness of the device"; Class II (requiring special controls or performance standards in addition to general controls in order to "provide reasonable assurance of the safety and effectiveness" of the device); and Class III (requiring pre-market approval because insufficient information exists to determine that general controls and special controls provide assurance

of safety and effectiveness and the devices are life-supporting or life-sustaining).[51]

4. Veterinary medical devices are under the regulatory jurisdiction of FDA CVM.[41,42]
5. FDA CVM "can take appropriate regulatory action if a veterinary device is misbranded, mislabeled, or adulterated" and recommends "that manufacturers and/or distributors of veterinary medical devices request a review of their product labeling and promotional literature to ensure that it complies with labeling and regulations."[42,43]
6. None of the regulations applied to human medical devices in Title 21 CFR Parts Part 860 (Medical Device Classification Procedures), 807 (Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices), 814 (Pre-market Approval of Medical Devices), 812 (Investigational Device Exemptions), 820 (Quality System Regulation), 801 (Labeling), 803 (Medical Device Reporting), 821 (Medical Device Tracking Requirements), and 822 (Postmarket Surveillance) are necessarily applied to veterinary medical devices by CVM.[9,51,55,59-65]
7. FDA CVM maintains documented reports of voluntarily reported adverse event clinical signs and product defects for veterinary medical devices that are identical or similar to human medical devices.[76]
8. Results from the qualitative risk assessment documented in Chapter 4 on nine (9) examples of medical devices used in both human and

veterinary applications demonstrated medium to high risk magnitude (on a low-medium-high scale) relative to veterinary medical device safety and effectiveness when specific parts of human medical device regulation are not applied.

Discussion

Research findings identified above answer the research questions posed in Chapter 1 and support the hypothesis presented in Chapter 3. Specifically, findings indicate that although veterinary medical devices are regulated as medical devices under the FD&C Act, there is considerably less regulation for veterinary medical device pre-market clearance, manufacturing control and post-market surveillance. FDA CVM has jurisdiction over veterinary medical devices and can take enforcement action if it makes a determination of misbranding, adulteration, or mislabeling of veterinary medical devices, but it does not enforce Title 21 Parts applicable to human medical device pre-market clearance, manufacturing, and post-market surveillance despite the fact that Title 21 CFR Subparts applicable to pre-market clearance, manufacturing controls, and post-market surveillance are intended to ensure device safety and effectiveness.[41-43] FDA CVM may expect that veterinary device manufacturers and distributors will use Title 21 CFR Part 820 as a guide to the manufacture and assembly of their devices, but veterinary devices are not specifically included within the scope of that regulation and therefore, as established in the risk assessment discussed below, are subject to the risk of not being safe or effective. FDA CVM's Cumulative Veterinary ADE Reports database for veterinary medical devices

contains documented evidence of adverse events and product defects voluntarily reported from the field, demonstrating that whether human medical device cGMPs discussed in the research are applied by veterinary medical device manufacturers and distributors or not, device safety and effectiveness is questionable, particularly relative to the specific devices assessed in the previous chapter.

The qualitative risk assessment performed as part of this research further demonstrates the magnitude of risk associated with not applying specific human medical device regulation to veterinary medical devices. This exercise assumed that for each device selected (as assigned by human medical device class), the risk classification for severity was always high when Title 21 CFR Subparts applicable to human medical device pre-market clearance, manufacturing controls, and post-market surveillance are not applied to veterinary devices. This assumption was made since these regulations are intended to ensure device safety and effectiveness, and would not be required if safety and effectiveness were not at risk. This exercise also assigned occurrence risk classifications based on evidence of occurrence of human medical device AEs or veterinary medical device AE clinical signs or quality defects. By factoring both severity and occurrence, a risk magnitude was identified for each of the nine (9) devices assessed, indicating that in the majority of these cases veterinary medical device safety and effectiveness are at high risk from a qualitative perspective. Table 4.24 summarized these findings.

Research findings support the hypothesis that:

- There is considerably less regulation for veterinary medical devices than human medical devices, which potentially puts both animal health and human health at risk;
- FDA's current approach to regulation of veterinary medical devices is insufficient to ensure that veterinary medical devices are safe and effective;
- Applying identical regulations and requirements to all classes of veterinary devices may not be appropriate in consideration of differences among target species and risk to safety and effectiveness relative to companion and production animals; and
- More clear and robust regulation of veterinary medical devices will put animal safety and veterinary device effectiveness at less risk, particularly if current science- and risk-based methodologies in human medical device regulation are applied to all classes of medical devices for various target species.

Table 5.1 assigns specific research findings to each component of the hypothesis which they support.

Table 5.1. Research Findings Which Support the Hypothesis

Hypothesis Components	Supporting Research Findings
Although human and veterinary medical devices are both regulated by the US FDA, and both are expected to be safe and effective, there is considerably less regulation for veterinary medical device approval, manufacturing control, and post-market surveillance, which potentially puts both animal health and human health at risk by permitting potentially unsafe veterinary medical devices to be marketed without FDA review.	• Human medical devices are under the regulatory jurisdiction of CDRH, as well as other Centers depending on the device's primary mode of action. • Veterinary medical devices are defined in the FD&C Act as medical devices and are therefore subject to regulation by FDA. • Veterinary medical devices are under the regulatory jurisdiction of CVM. • FDA CVM "can take appropriate regulatory action if a veterinary device is misbranded, mislabeled, or adulterated" and does recommend "that manufacturers and/or distributors of veterinary medical devices request a review of their product labeling and promotional literature to ensure that it complies with labeling and regulations." • None of the regulations applied to human medical devices in Title 21 CFR Parts 860 (Medical Device Classification Procedures), 807 (Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices), 814 (Pre-market Approval of Medical Devices), 812 (Investigational Device Exemptions), 820 (Quality System Regulation), 801 (Labeling), 803 (Medical Device Reporting), 821 (Medical Device Tracking Requirements), and 822 (Postmarket Surveillance) are necessarily applied to veterinary medical devices by CVM.
FDA's current approach to regulation of veterinary medical devices is insufficient to ensure that veterinary medical devices are safe and effective.	• None of the regulations applied to human medical devices in Title 21 CFR Parts 860 (Medical Device Classification Procedures), 807 (Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices), 814 (Pre-market Approval of Medical Devices), 812 (Investigational Device Exemptions), 820 (Quality System Regulation), 801 (Labeling), 803 (Medical Device Reporting), 821 (Medical Device Tracking Requirements), and 822 (Postmarket

Hypothesis Components	Supporting Research Findings
	Surveillance) are necessarily applied to veterinary medical devices by CVM. • FDA CVM maintains documented reports of voluntarily reported adverse event clinical signs and product defects for veterinary medical devices that are identical or similar to human medical devices. • Results from the qualitative risk assessment performed in Chapter 3 on nine (9) examples of medical devices used in both human and veterinary applications demonstrated medium to high risk magnitude (on a low-medium-high scale) relative to veterinary medical device safety and effectiveness when specific parts of human medical device regulation are not applied.
Applying identical regulations and requirements to all classes of veterinary devices may not be appropriate in consideration of differences among target species and risk to safety and effectiveness.	• Human medical devices are assigned to device classifications of Class I, Class II, or Class III depending on the level of information available for reasonable assurance of safety and effectiveness in order to define pre-market clearance, manufacturing control, and post-market surveillance requirements.
More clear and robust regulation of veterinary medical devices will put animal safety and veterinary device effectiveness at less risk, particularly if current science- and risk-based methodologies in human medical device regulation are applied to all classes of medical devices for various target species.	• Results from the qualitative risk assessment performed in Chapter 3 on nine (9) examples of medical devices used in both human and veterinary applications demonstrated medium to high risk magnitude (on a low-medium-high scale) relative to veterinary medical device safety and effectiveness when specific parts of human medical device regulation are not applied.

The research hypothesis is consistent with the review of the literature summarized in Chapter 2. Specific regulatory documents and laws do not conclude or state that not applying human medical device regulation to veterinary devices presents risk, but statements that FDA has made on their website and in verbal communication support the research hypothesis and subsequent findings. The review of the literature summarized FDAs dedication to protecting human and animal health. However, the review of the literature also demonstrated that despite the inclusion of regulation of human and veterinary medical devices in the 1938 FD&C Act, cGMPs for human medical devices were not actually promulgated until 1978. Therefore, although clear gaps between human and medical device regulation have been indentified in the research, human and veterinary devices shared a forty (40) year hiatus from cGMPs. But it has now been 75 years since the passage of the 1938 Act, and it seems uncharacteristic of FDA to understand that there is a gap in regulation relative to veterinary medical devices which has a demonstrated effect on safety and effectiveness and not have already acted on it through further development of regulation or guidance documents.

Given that specific regulations created for application to human medical devices for control of pre-market clearance, manufacturing, and post-market surveillance in order to ensure device safety and effectiveness are not applied to veterinary medical devices, it has been established through this research that there is risk to veterinary medical device safety and effectiveness. Furthermore, based on the criteria and method of risk assessment applied in this research, the

level of risk associated with not applying specific human medical device regulations to veterinary medical devices is relatively high.

Conclusion

This research considered the development and passage of specific US laws passed as early as 1813 and their impact on the development of the agencies which today regulate human and veterinary drugs, biologics, devices, and combination products, as well as the application of specific medical device regulation relative to human and veterinary medical devices. A qualitative comparison of regulations applied to human and veterinary medical devices and a subsequent risk assessment of the specific gaps in application of these regulations were performed in order to identify potential risk to animal safety and veterinary device effectiveness, as well as potential risk to human health.

Veterinary medical devices are used to perform very basic sanitary functions to very complex and life-sustaining functions in both companion and production animals, from dental wax and surgical gloves, to hip replacement prostheses and pacemakers. Some veterinary medical devices lend themselves to application in companion animals, whose owners may expect quality and safety. But veterinary medical devices are also used to support production animal vaccination and parasiticide programs in order to protect animal and human health, as well as to protect the US human food supply. Certain residues of in-vivo diagnostics or metal syringe tips can remain in food animal tissue and subsequently contaminate food. Non-sterile injectors are commonly used with sterile injectable products in the food animal industry. There are many factors to

consider when evaluating the variability in regulatory requirements for pre-market clearance, manufacturing control, and post-market surveillance of human and veterinary medical devices in the United States, and this research supports the hypothesis that FDA's current approach to regulation of veterinary medical devices is insufficient to ensure that veterinary medical devices are safe and effective.

Recommendations

The findings and conclusion of this research support recommendations to FDA, industry, and academia. Considering that it may not be possible to initiate actions following these recommendations simultaneously or in parallel, recommendations are listed in a proposed order of priority such that immediate needs may be identified and most significant risk to veterinary medical device safety and effectiveness may be mitigated:

1. Veterinary medical device adverse event reporting should be required in order to assess the true impact of veterinary medical device safety and effectiveness relative to companion and production animals and the human population impacted by the use of unsafe or ineffective devices on food-producing animals. Mandatory veterinary medical device adverse event reporting will identify devices with the most significant or most frequently reported issues in terms of safety and effectiveness, providing a primary target population of devices which require closer scrutiny.

2. CDRH and CVM should consider including the veterinary health community (veterinarians, clinicians, drug and device manufacturers, and end users) in their current evaluation of how CVM specifically regulates veterinary medical devices.
3. An inventory of veterinary medical devices marketed in the US should be developed, whether as a result of application of establishment and device listing regulation or independent investigation in order to determine the scope of impact if medical device regulations were applied to veterinary medical devices.
4. An assessment of the impact of possible user fees for veterinary medical device review and/or approval on manufacturers and distributors should be performed in order to understand what financial impact such regulation would have on the availability of such devices.
5. Whether user fees are established for veterinary medical devices or not, an independent assessment of CDRH/CVM enforcement capabilities should be performed. Establishing specific requirements for pre-market clearance, manufacturing, and post-market surveillance may not result in risk reduction if enforcement is not sufficiently financed.
6. Pre-market clearance of veterinary medical devices should be required in order to prevent distribution of mislabeled, misbranded, or adulterated devices.

7. Human medical device regulation should be applied to veterinary medical devices, or at least applied according to risk of impact to human safety, or specific regulations applicable to veterinary medical devices should be promulgated.
8. The development of regulation and guidance for combination products must also take into account their applicability to veterinary combination products.
9. The gap assessment and supporting risk assessment performed in this research identified that there is significant risk to veterinary medical device safety and effectiveness impacting animals and humans, but more precise and extensive evaluation of the gaps and associated risk is warranted.
    a. The qualitative risk assessment performed in this research would not necessarily establish to what level myriad veterinary medical devices should comply with specific regulation applied to human medical devices.
    b. Quantitative risk assessments may provide greater accuracy than qualitative risk assessments. A quantitative risk assessment exercise evaluating the commonly used factors of severity, frequency, and detectability was not feasible in this research because:
        - Frequency of adverse event clinical signs occurring in the field temporal to the use of veterinary medical

devices is mostly unknown because reporting these events in animals is not mandatory.[42] Physiological differences in species and unknown rates of distribution of veterinary medical devices prevent accurate extrapolation of the frequency of adverse event clinical signs in humans to the frequency of adverse event clinical signs in animals.

- Detectability is unreliable because animals cannot explain pain or symptoms and are often stoic, despite their ability to vocalize or display symptoms such as lethargy, grooming, lameness, infection, and mortality.[93] While veterinarians, clinicians and pet owners could likely detect many adverse event clinical signs through physical or bioanalytical examination, the application of detectability in this risk assessment would be subjective.[93]

10. Further research studying the variability in human and veterinary drug, biologic, medical device, and combination product requirements for pre-market clearance or approval, manufacturing controls, and post-market surveillance should be conducted in light of the inconsistent regulatory approaches to all classes of drugs and devices identified in the review of the literature.

REFERENCES

[1] United States Code, 2010 Edition. Title 21 - FOOD AND DRUGS. CHAPTER 9 - FEDERAL FOOD, DRUG, AND COSMETIC ACT. SUBCHAPTER V - DRUGS AND DEVICES. Part A - Drugs and Devices. Sec. 360e – Pre-market approval. From the U.S. Government Printing Office. http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360e.htm. Accessed on 27 January 2013.

[2] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 807 ESTABLISHMENT REGISTRATION AND DEVICE LISTING FOR MANUFACTURERS AND INITIAL IMPORTERS OF DEVICES. Revised as of April 1, 2012. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807&showFR=1&subpartNode=21:8.0.1.1.5.5. Accessed 27 January 2013.

[3] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 820 QUALITY SYSTEM REGULATION. Revised as of April 1, 2012. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820. Accessed 27 January 2013.

[4] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER E--ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS. PART 514 -- NEW ANIMAL DRUG APPLICATIONS. Subpart B--Administrative Actions on Applications Sec. 514.80 Records and reports concerning experience with approved new animal drugs. Revised as of April 1, 2012. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=514.80. Accessed 27 January 2013.

[5] Committee on the National Needs for Research in Veterinary Science, National Research Council. Critical Needs for Research in Veterinary Science. 2005. http://www.nap.edu/openbook.php?record_id=11366&page=R1. Accessed 27 January 2013.

[6] PMA database. US Department of Health and Human Services. US FDA. Medical Devices. PMA Approvals. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Accessed 27 January 2013.

[7] Downloadable 510(k) files. US Department of Health and Human Services. US FDA. Medical Devices.

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm089428.htm. Accessed 27 January 2013.

[8] US Department of Health and Human Services. US FDA. Medical Devices. Pre-market Notification (510k). http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm. Accessed 27 January 2013.

[9] FDA Veterinarian Newsletter May/June 2003 Volume XVIII, No 3. US Department of Health and Human Services. US FDA. Animal & Veterinary. How FDA Regulates Veterinary Devices. http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm102701.htm. Accessed 27 January 2013.

[10] Junod S. *FDA: A History* [DVD]. Compliance Media; 2008.

[11] Swann J. US Department of Health and Human Services. US FDA. About FDA. FDA's Origin. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm. Accessed 01 February 2013.

[12] Meadows M. US Department of Health and Human Services. US FDA. About FDA. Promoting Safe and Effective Drugs for 100 Years. http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDAConsumer/ucm093787.htm. Accessed 01 February 2013.

[13] US Department of Health and Human Services. US FDA. About FDA. FDA History – Part I. The 1906 Food and Drugs Act and Its Enforcement. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm. Accessed 01 February 2013.

[14] Spiegel M. In discussion of: Sinclair U. *The Jungle.* New York, NY: Barnes and Noble Books; 2003.

[15] Morris, E. *The Rise of Theodore Roosevelt.* New York, NY: The Modern Library; 2001.

[16] US Department of Health and Human Services. US FDA. About FDA. Significant Dates in U.S. Food and Drug Law History. http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm. Accessed 01 February 2013.

[17] Erickson M. *FDA: A History* [DVD]. Compliance Media; 2008.

[18] US Department of Health and Human Services. US FDA. About FDA. FDA History – Part II. The 1938 Food, Drug, and Cosmetic Act. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054826.htm. Accessed 01 February 2013.

[19] Zoon K, Yetter A. The Regulation of Drugs and Biological Products by the Food and Drug Administration. In: Gallin J, Ognibene F, eds. *Principles and Practice of Clinical Research*. 2nd ed. Burlington, MA: Academic Press; 2007: 97.

[20] Junod S. History of FDA. Presented at:35th International Good Manufacturing Conference; March 2011; Athens, GA.

[21] US Department of Health and Human Services. US FDA. About FDA. FDA History – Part III. Drugs and Foods Under the 1938 Act and Its Amendments. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm055118.htm. Accessed 01 February 2013.
[22] US Department of Health and Human Services. US FDA. About FDA. FDA History – Part V. Trends in the Last Quarter-Century. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm125632.htm. Accessed 01 February 2013.
[23] 21 U.S.C. United States Code, 2010 Edition. Title 21 - FOOD AND DRUGS. CHAPTER 9 - FEDERAL FOOD, DRUG, AND COSMETIC ACT. SUBCHAPTER II – DEFINITIONS. http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapII.htm. Accessed 02 February 2013.
[24] US Department of Health and Human Services. US FDA. About FDA. The Road to the Biotech Revolution - Highlights of 100 Years of Biologics Regulation. http://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/CBER/ucm135758.htm. Accessed 02 February 2013.
[25] US Department of Health and Human Services. US FDA. Vaccines, Blood & Biologics. http://www.fda.gov/BiologicsBloodVaccines/default.htm. Accessed 02 February 2013.
[26] US Department of Health and Human Services. US FDA. Vaccines, Blood & Biologics. Influenza Virus Vaccine Composition and Lot Release. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm062928.htm. Accessed 02 February 2013.
[27] US Department of Health and Human Services. US FDA. Vaccines, Blood & Biologics. VAERS Overview. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/VaccineAdverseEvents/Overview/default.htm. Accessed 02 February 2013.
[28] Termini R. *Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements.* 3rd ed. Wynnewood, PA: FORTI Publications; 2007:120-121.
[29] US Department of Health and Human Services. US FDA. About FDA. Medical Device and Radiological Health Regulations Come of Age. http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/MedicalDeviceandRadiologicalHealthRegulationsComeofAge/default.htm. Accessed 02 February 2013.
[30] US Department of Health and Human Services. US FDA. About FDA. FDA History – Part IV. Regulating Cosmetics, Devices, and Veterinary Medicine After 1938. http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm055137.htm. Accessed 02 February 2013.
[31] US Department of Health and Human Services. US FDA. Home. Medical Devices. Device Advice: Comprehensive Regulatory Assistance. Postmarket Requirements (Medical Devices).

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm. Accessed 30 March 2013.
[32] Mullis D. Combination Products Regulatory Overview. Presented at: PHARM 6010; University of Georgia Graduate School; Introduction to Pharmaceutical, Biotechnology and Device Regulatory Affairs lecture; 2007.
[33] 78 FR 4307. Current Good Manufacturing Practice Requirements for Combination Products. A Rule by the Food and Drug Administration on 01/22/2013. https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. Accessed 30 March 2013.
[34] Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA. U.S. Department of Health and Human Services, Food and Drug Administration, Office of Combination Products, Office of Special Medical Programs, Office of the Commissioner. January 2013. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336230.pdf. Accessed 30 March 2013.
[35] Termini R. *Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements.* 3rd ed. Wynnewood, PA: FORTI Publications; 2007: 351.
[36] Termini R. *Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements.* 3rd ed. Wynnewood, PA: FORTI Publications; 2007: 351,354.
[37] Termini R. *Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements.* 3rd ed. Wynnewood, PA: FORTI Publications; 2007: 352.
[38] United States Department of Agriculture. Animal and Plant Health Inspection Service. About APHIS. History of APHIS. http://www.aphis.usda.gov/about_aphis/history.shtml. Accessed 03 February 2013.
[39] *A 40-Year Retrospective of APHIS, 1972–2012*. United States Department of Agriculture. Animal and Plant Health Inspection Service. http://www.aphis.usda.gov/about_aphis/downloads/40_Year_Retrospective.pdf. Accessed 03 February 2013.
[40] *Veterinary Biologics: Use and Regulation*. United States Department of Agriculture. Animal and Plant Health Inspection Service. Revised February 2013. http://www.aphis.usda.gov/publications/animal_health/content/printable_version/vet_biologics.pdf. Accessed 10 February 2013.
[41] TITLE 21. FOOD AND DRUGS CHAPTER 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT. SUBCHAPTER II DEFINITIONS. 21 USC§ 321. Definitions; generally, 21 USC § 321 (2006).
[42] US Department of Health and Human Services. US FDA. Animal & Veterinary. How FDA Regulates Veterinary Devices. http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm102701.htm. Accessed 16 February 2013.

[43] US Department of Health and Human Services. US FDA. Inspections, Compliance, Enforcement, and Criminal Investigations. CPG Sec. 607.100 - Adequate Directions for Use (Species Designation) - Animal Drugs and Veterinary Devices. http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074652.htm. Accessed 16 February 2013.

[44] US Department of Health and Human Services. US FDA. Inspections, Compliance, Enforcement, and Criminal Investigations. Anchor Products Company, Inc 11/8/10. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm234624.htm. Accessed 16 February 2013.

[45] US Department of Health and Human Services. US FDA. Inspections, Compliance, Enforcement, and Criminal Investigations. Engler Engineering Corporation 20-Jul-01. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2001/ucm178482.htm. Accessed 16 February 2013.

[46] US Department of Health and Human Services. US FDA. Animal & Veterinary. FDA Warns of Possible Danger with Animal Vaccine Device. http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm270642.htm. Accessed 16 February 2013.

[47] Termini R. Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements. 3rd ed. Wynnewood, PA: FORTI Publications; 2007: 120.

[48] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H- L. Current as of 21 February 2013. http://www.ecfr.gov/cgi-bin/text-idx?SID=2d4a22ab081ca5d6da764f0280ff3925&c=ecfr&tpl=/ecfrbrowse/Title21/21cfrv8_02.tpl. Accessed 23 February 2013.

[49] US Department of Health and Human Services. US FDA. Medical Devices. Device Advice: Comprehensive Regulatory Assistance. Overview of Device Regulation. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm. Accessed 23 February 2013.

[50] US Department of Health and Human Services. US FDA. Medical Devices. Device Advice: Comprehensive Regulatory Assistance. Classify Your Medical Device. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm. Accessed 23 February 2013.

[51] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 860. Medical Device Classification Procedures. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=2d4a22ab081ca5d6da764f0280ff3925&rgn=div5&view=text&node=21:8.0.1.1.15&idno=21. Accessed 23 February 2013.

[52] *Class II Special Controls Guidance Document: Indwelling Blood Gas Analyzers; Final Guidance for Industry and FDA*. CDRH. Document issued on: October 5, 2001. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073413.htm. Accessed 30 March 2013.

[53] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. Sec. 878.4010 Tissue adhesive. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=a6ca3f112370c5eea2d771365e74a556&rgn=div5&view=text&node=21:8.0.1.1.25&idno=21. Accessed 02 March 2013.

[54] US Department of Health and Human Services. US FDA. Medical Devices. Device Advice: How to Market Your Device. Premarket Approval (PMA). http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm. Accessed 30 March 2013.

[55] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 807. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=036a6f369dae81aa84ff0c8fa96b7121&rgn=div5&view=text&node=21:8.0.1.1.5&idno=21. Accessed 23 February 2013.

[56] US Department of Health and Human Services. US FDA. Medical Devices. Premarket Notification (510k). http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm. Accessed 23 February 2013.

[57] *The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications.* US Department of Health and Human Services. Food and Drug Administration. Center for Devices and Radiological Health. Rockville, MD: 1998. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm/. Accessed 23 February 2013.

[58] Termini R. Life Sciences Law: Federal Regulation of Drugs, Biologics, Medical Devices, Foods and Dietary Supplements. 3rd ed. Wynnewood, PA: FORTI Publications; 2007: 132.

[59] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 814. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=2d4a22ab081ca5d6da764f0280ff3925&rgn=div5&view=text&node=21:8.0.1.1.11&idno=21. Accessed 24 February 2013.

[60] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 812.

INVESTIGATIONAL DEVICE EXEMPTIONS. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=9acf61d81666073060d13715bfe9f3cb&rgn=div5&view=text&node=21:8.0.1.1.9&idno=21. Accessed 24 February 2013.

[61] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 820 QUALITY SYSTEM REGULATION. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=9acf61d81666073060d13715bfe9f3cb&rgn=div5&view=text&node=21:8.0.1.1.12&idno=21. Accessed 24 February 2013.

[62] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 801. Labeling. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=9acf61d81666073060d13715bfe9f3cb&rgn=div5&view=text&node=21:8.0.1.1.2&idno=21. Accessed 24 February 2013.

[63] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 803. Medical Device Reporting. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=9acf61d81666073060d13715bfe9f3cb&rgn=div5&view=text&node=21:8.0.1.1.3&idno=21. Accessed 25 February 2013.

[64] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 821. Medical Device Tracking Requirements. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=9acf61d81666073060d13715bfe9f3cb&rgn=div5&view=text&node=21:8.0.1.1.13&idno=21. Accessed 25 February 2013.

[65] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. PART 822. Postmarket Surveillance. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=9acf61d81666073060d13715bfe9f3cb&rgn=div5&view=text&node=21:8.0.1.1.14&idno=21. Accessed 25 February 2013.

[66] Broken needles found in pork at Manitoba packing plant. CBC News Posted: Jan 24, 2013. http://www.cbc.ca/news/canada/manitoba/story/2013/01/23/mb-pork-needles-fragments-packing.html. Accessed 24 March 2013.

[67] US Department of Health and Human Services. US FDA. Warning Letters and Responses. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm. Accessed 25 February 2013.

[68] MacIntire SJ. Warning Letter issued to Anchor Products Company, Inc. by FDA Chicago District Office on 08 November 2010. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm234624.htm. Accessed 25 February 2013.

[69] Silverman SD. Warning Letter issued to ARC Medical Supplies (Beijing) Co., Ltd. by FDA CDRH on 28 March 2011. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm250174.htm. Accessed 25 February 2013.
[70] Heppe CA. Warning Letter issued to E-Med Future, Inc. by FDA Cincinnati District Office on 08 January 2003. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2003/ucm147257.htm. Accessed 25 February 2013.
[71] Singleton E. Warning Letter issued to Engler Engineering Corporation by FDA Florida District Office on 20 July 2001. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2001/ucm178482.htm. Accessed 25 February 2013.
[72] Cruse AE. Warning Letter issued to Innovacyn, Inc. by FDA Los Angeles District Office on 23 July 2012. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm315117.htm. Accessed 25 February 2013.
[73] MacIntire SJ. Warning Letter issued to Macan Engineering and Manufacturing Company Inc. by FDA Chicago District Office on 15 September 2005. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2005/ucm075563.htm. Accessed 25 February 2013.
[74] Spears LD. Warning Letter issued to SEDECAL SA (Sociedad Espaloa de Electromedicine y Calidad S.A.) by FDA CDRH on 05 July 2001. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2001/ucm178245.htm. Accessed 25 February 2013.
[75] Costello GT. Warning Letter issued to Wallach Surgical Devices, Inc. by FDA New England District Office on 03 August 2006. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076018.htm. Accessed 25 February 2013.
[76] *CVM ADE Comprehensive Clinical Detail Report Listing: Cumulative Date Range: 01/01/1987 -thru- 02/28/2013 Drug Listing: D;E;F;G;H;I.* US Department of Health and Human Services. US FDA: 2013; 64-76. http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055369.htm. Accessed 25 February 2013.
[77] US Department of Health and Human Services. US FDA. Medical Devices Device Advice: Comprehensive Regulatory Assistance. Postmarket Requirements (Medical Devices). Reporting Adverse Events (Medical Devices). http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/default.htm. Accessed 30 march 2013.
[78] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. Section 872.6890 Intraoral dental wax. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=0be98add4abeff548f86c9ccbc6a7d3b&rgn=div5&view=text&node=21:8.0.1.1.22&idno=21#21:8.0.1.1.22.7.1.28. Accessed 02 March 2013.

[79] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. Section 878.4014 Nonresorbable gauze/sponge for external use. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=a6ca3f112370c5eea2d771365e74a556&rgn=div5&view=text&node=21:8.0.1.1.25&idno=21. Accessed 02 March 2013.

[80] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. Sec. 878.4010 Tissue adhesive. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=a6ca3f112370c5eea2d771365e74a556&rgn=div5&view=text&node=21:8.0.1.1.25&idno=21. Accessed 02 March 2013.

[81] US DEPARTMENT OF HEALTH AND HUMAN SERVICES. U.S. Code of Federal Regulations. Title 21, Volume 8. CHAPTER I--FOOD AND DRUG ADMINISTRATION. SUBCHAPTER H--MEDICAL DEVICES. Sec. 888.3300 Hip joint metal constrained cemented or uncemented prosthesis. http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=a6ca3f112370c5eea2d771365e74a556&rgn=div5&view=text&node=21:8.0.1.1.30&idno=21#21:8.0.1.1.30.4.1.25. Accessed 03 March 2013.

[82] Legget D. Lab-HIRA: Hazard identification and risk analysis for the chemical research laboratory. Part 2. Risk analysis of laboratory operations. Journal of Chemical Health and Safety. Volume 19, Issue 5, September–October 2012: 25–36. http://www.sciencedirect.com/science/article/pii/S187155321200014X. Accessed 23 March 2013.

[83] Health and Safety Executive. HSE. Guidance. Topics. Risk management. FAQs. http://www.hse.gov.uk/risk/faq.htm. Accessed 23 March 2013.

[84] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: “dental wax”, All years. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 02 March 2013.

[85] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: Device: Surgeon's Gloves Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 02 March 2013.

[86] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: Device: Gauze/Sponge,Nonresorbable For External Use”, Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 02 March 2013.

[87] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search

criteria: Device: Tissue Adhesive for the Topical Approximation of Skin. Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 02 March 2013.

[88] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: "fluid injector", All years. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 02 March 2013.

[89] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: Device: Syringe, piston. Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 02 March 2013.

[90] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: Device: Implantable Pacemaker Pulse Generators. Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 03 March 2013.

[91] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: Device: Prosthesis, Hip, Constrained, Metal. Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 03 March 2013.

[92] US Department of Health and Human Services. US FDA. Medical Devices. Databases. Manufacturer and User Facility Device Experience (MAUDE). Search criteria: Device: Intraocular lens. Report Date From: 01/01/1990 Report Date To: 01/31/2013. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm. Accessed 03 March 2013.

[93] Kahn C, ed. The Merck Veterinary Manual. 9th ed. Whitehouse Station, NJ:Merck & Co., Inc.; 2005:1691-1694.