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What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis

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Edward L. Korwek, Ph.D., J.D.*

Double, double toil and trouble;
Fire burn, and caldron bubble . . . .
Fillet of a fenny snake,
In the caldron boil an bake;
Eye of newt, and toe of frog,
Wool of bat, and tongue of dog,
Adder's fork, and blind-worm's sting,
Lizard's leg, and owlet's wing.
Macbeth

I. Introduction

Biologics are often described as vaccines, blood products (including blood) and allergenics. Since the late 1940s, however, the types of products that are biologics have been expanding. The advent of modern biotechnology methods in the last 25 years has contributed dramatically to this expansion. Hybridoma and recombinant DNA methods, gene and cellular therapies, and newer technologies, such as the cloning method involved in the creation of Dolly the Sheep in 1996,[1] have challenged traditional notions of what are biologics.[2] The new technologies also have recently resulted in questions of by whom and how biologics should be regulated vis-à-vis other drugs handled by the Center for Drug Evaluation and Research (CDER)[3] or the Center for Veterinary Medicine (CVM).

Biologics are often distinguished today in terms of their sources, chemical properties, immunogenicity,[4] macromolecular size or structure, or how they function. They have been characterized as complex macromolecules, as proteins, or as derived from living organisms or natural sources, as difficult to identify compared to so-called small molecule drugs, or as generally working through some immune mechanism or process.[5] These descriptions can also vary, depending on one's vantage point,

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[1] *See* I. Wilmut et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, 385 Nature 810 (1997). *See also* K.H.S. Campbell et al., *Sheep Cloned by Nuclear Transfer from a Cultured Cell Line*, 380 Nature 64 (1996).

[2] *See, e.g.*, Stuart L. Nightingale, *Emerging Technologies in FDA Policy Formulation: The Impact of Government Regulation in Developing Drugs From New Technologies*, 37 Food Drug Cosm. L.J. 212 (1982).

[3] Many therapeutic biologics were transferred in 2003 from the Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). *See infra* note 100 and accompanying text.

[4] M. Wadhwa & R. Thorpe, *Unwanted Immunogenicity: Implications for Follow-On Biologicals* 41 Drug Info. J. 1 (2007); Thomas Morrow, *Defining the Difference: What Makes Biologics Unique*, Biotechnology Healthcare 25 (Sept. 2004).

[5] *See, e.g.,* FDA, CDER, Frequently Asked Questions About Therapeutic Biological Products, What Is a Biological Product?, *at* http://www.fda.gov/cder/biologics/qa.htm, and CVM Biologics, Frequently Asked Questions, What Are Veterinary Biologics?, *at* http://www.aphis.usda.gov/vs/cvb/html/lpdfaqs.html. *See also* Annabel Hecht, *Making Sure Biologicals Are Safe*, FDA Consumer, (July-Aug. 1977) at 21 (stating that "[v]accines are … called 'biologics' because they are made from or with the aid of living organisms that are produced in man or animals").

as a physician, lawyer, molecular biologist, endocrinologist, immunologist, or immunochemist, for example.[6] The author's purpose here is to try to clarify the nature of biologics in a legal sense with some related scientific elaboration. The language of biologics is steeped in the history and science of immunization.

The subject of this article has been addressed in various contexts.[7] This presentation is very different. It involves a variety of diverse comparisons, primarily relating to the similarities and differences between human biologics and their veterinary counterparts. Although this approach may seem unusual, several reasons exist for making such comparisons. Another contrast involves the changes in the federal statutory and regulatory language describing or defining biologics as such language has evolved over the last one hundred years. Accompanying these and other analyses is some further technical commentary involving medical and other technological advances relating to past or modern-day interpretations of what biologics are and are not.

The specific discussions are organized into three broad categories or topic areas. The first involves the history of the relevant statutes and regulations, which focuses on the significant changes in the definitions of human and veterinary biologics. Also provided are some explanations for or commentary on such changes. The next category is a review of important agency initiatives during the modern biotechnology era that did or did not embrace the definitions for biologics. Such initiatives include those governing gene and cell therapy, tissue regulation, and cloning. The last topic contains a few final observations and perspectives about the different agency "recipes" for biologics.

The presentation is largely chronological, but overlap exists. The emphasis is on the prophylactic and curative nonblood uses of biologics in human beings and other animals, not on their *in vitro* utility involving, for example, diagnostics or other uses pertaining to device status. To assist the reader in understanding and following the historical evolution of the biological product definitions, three tables are attached at the end of this article. Each tracks the significant changes in the relevant statutory and regulatory definitions, by showing deleted (crossed out) or added (underscored) language, or both. Editorial or other minor modifications are not separately covered but are reflected when the next major revisions occurred.

Table I covers the major changes in the statutory definition for a human biologic over the last one hundred years. No corresponding table tracks veterinary statutory changes because the definitional provisions have not been altered substantively in the past 85 years. Table II describes the evolution of the regulatory definitions for human biologics, and Table III addresses the key revisions of the veterinary biological regulatory definitions.

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[6] *See, e.g.*, K. Katz, Editorial, *'Biologics': A Clinically Meaningless Term*, 154 BRIT. J. DERMATOL. 809 (2006) (noting that medical and legal definitions of the term "biologics" vary significantly).

[7] *See, e.g.*, Steven R. Scott, *What Is a Biologic?*, *in* BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW, ch. 1 (Parexel Int. Corp. 3d ed. 2004). *See also* Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 FOOD & DRUG L.J. 123 (1995).

One of the major issues in human biologics regulation today is the topic of "generic" or follow-on versions. *See, e.g.*, Edward L. Korwek, *Towards Understanding the "Generic" Debate about Biologics,* 7 J. BIOLAW & BUS. 27 (2004) and Janet Woodcock, et al., *Perspectives, The FDA's Assessment of Follow-on Protein Products; A Historical Perspective*, 6 NATURE REVIEWS DRUG DISCOVERY, Advance Online Publication (Apr. 13, 2007), *available at* www.nature.com/nrd/index.html. *See also* David M. Dudzinski, Reflections on Historical, Scientific and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies, 60 FOOD & DRUG L. J. 143 (2005); Donald E. Segal et al., *Regulatory Pathway for "Biosimilar" Products Debated*, 22 WASHINGTON LEGAL FOUNDATION, LEGAL BACKGROUNDER, no. 6 (2007); and Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77 (2007).

II. BACKGROUND

Human and other animal biologics have always been the subject of two separate statutes administered by two different federal agencies. The Food and Drug Administration (FDA) regulates human biologics principally under section 351 of the Public Health Service Act (PHSA);[8] implementing regulations appear in Title 21 of the Code of Federal Regulations.[9] Veterinary biologics are regulated by the Animal Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) under the Virus Serum Toxin Act (VSTA)[10] and implementing regulations in Title 9.[11]

Both statutes and sets of regulations contain two different, basic criteria that must be met to qualify as a biologic. One criterion or prong relates to the descriptions or definitions of the types of products that are covered. For purposes of this article, this criterion is called the "subject matter" of the statutes or regulations. The second prong involves the medical use of such products or the "use" provisions. The emphasis is often on the former criterion, rather than the latter.

The current human and veterinary provisions can be traced back to two very similar laws covering the same subject matter enacted in 1902 and 1913, respectively.[12] Although both statutes have been amended to varying degrees over the last one hundred years,[13] the provisions addressing covered human products have been substantively amended only three times (Table I). Since similar language in VSTA has not been amended at all, the listed products covered by the statute are the same as they were in 1913. On the other hand, both the human and veterinary regulatory provisions defining biologics have been substantively amended fairly often (Tables II and III).

Why numerous changes were made is unclear. The legislative and regulatory histories of many of the dated amendments and some of the newer ones, as evidenced in Congressional Reports, debates and available hearings, or in rulemaking proceedings, are often absent. Part of the reason for the lack of regulatory background is that the *Federal Register* was not published until 1936. Moreover, agency explanations for changes in its regulations did not begin to be published as part of the preamble language of the *Federal Register* until roughly 1976.[14] Prior to that time, all that was often said was that regulations were being amended in light of comments that had been submitted, without further elaboration.[15]

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[8] Pub. L. No. 572-44, ch. 1378, 32 Stat. 728 (July 1, 1902) (codified as amended at 42 U.S.C. §§ 262 et seq.).

[9] 21 C.F.R. pts. 600-680 (2006).

[10] Pub. L. No. 62-430, ch. 145, 37 Stat. 832 (Mar. 4, 1913) (codified as amended at 9 U.S.C. §§ 151 et seq.).

[11] 9 C.F.R. pts. 101-118, 123-124 (2006).

[12] Statutes involving the same subject matter should be construed in *pari materia*. *See* Burlington Northern and Santa Fe Ry. Company v. White, 126 S. Ct. 2405, 2411 (2006).

[13] *See, e.g.*, Food Security Act of 1985, Pub. L. No. 99-198, § 1768, 99 Stat. 1654 (1985) (amending the Virus Serum Toxin Act (VSTA) to regulate intrastate vaccines), and Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, § 123, 111 Stat. 2323 (Nov. 21, 1997) (modernization of regulation of biologics, including the elimination of license requirements for establishments). As alluded to earlier in the text, this article does not focus on all changes, but only on those pertaining to the definitions or descriptions of biologics.

[14] In 1973, final rules were required by the Administrative Committee of the Federal Register to have in their preambles a statement summarizing the general subject matter of the rule. Administrative Committee of the Federal Register, Revision of Regulations, 37 Fed. Reg. 23,602 (1972) (codified at 1 C.F.R. pts. 1-22). In 1977, comments to proposed rules and answers to them were required to be summarized in the preamble. Administrative Committee of the Federal Register, Preparation and Transmittal of Documents Generally, Clarity of Rulemaking Documents in the Federal Register, 41 Fed. Reg. 56,623 (1976) (codified at 1 C.F.R. § 18.12).

[15] *See, e.g.*, Public Health, Biological Products, Miscellaneous Amendments, 43 Fed. Reg. 367, 367 (1968) (stating, "After consideration of all the comments submitted … the Public Health Service regulations [are] hereby adopted to become effective thirty days after the date of publication in the Federal Register ….").

Despite the emphasis herein on specific biologics legislation and regulations, the importance of the Federal Food, Drug, and Cosmetic Act (FDCA)[16] cannot be overemphasized. This is in part because the definition of a "drug" is rather simple, particularly in comparison to the provisions applicable to biologics. Moreover, since the definitions in the FDCA are broad for a "drug" and a "device,"[17] various provisions of it have been applied to human and veterinary biologics, as biological drugs or biological devices.[18] Stated somewhat differently, the practical significance of this overlap is that products that do or do not qualify as biologics usually can be easily subject to the FDCA as devices or as human or veterinary drugs.[19] Indeed, this has been a recurrent theme of FDA's regulation of products of modern biotechnology methods.[20]

Also worth mentioning briefly is the evolution of the relevant federal bureaucracy. Until 1953 the Bureau of Animal Industry (BAI) within USDA regulated veterinary biologics through the issuance of BAI orders.[21] At that time, BAI became part of the Animal Health Division of the Agricultural Research Service and, in 1972, became part of the Veterinary Services unit of APHIS and, ultimately, the Center for Veterinary Biologics.[22]

The responsibility for human biologics regulation has also undergone several organizational rearrangements. Originally, the U.S. Public Health and Marine-Hospital Service, within the Department of Treasury, was involved; followed by the Division of Pathology and Bacteriology of the Hygienic Laboratory; then the Division of Biologics Control, which eventually was redesignated as the Laboratory of Biologics Control as part of the National Biological Institute, which was

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[16] Pub. L. No. 75-717, ch. 675, 52 Stat. 1040 (June 25, 1938) (as amended in 1962) (codified as amended at 21 U.S.C. §§ 301 et seq.).

[17] *See* FDCA § 201(g) and (h), 21 U.S.C. § 321(g) and (h). A drug is defined, in most relevant part, as any article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals. A device is defined as an instrument, apparatus, implement, machine, contraband, implant, in vitro reagent, or other similarly related article, including any component, part, or accessory that is 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 intended to affect the structure or function of the body of man or other animal. It cannot achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of its primary intended purposes.

[18] The intersection of the FDCA with VSTA and the biological provisions of the PHSA, a topic that is beyond the scope of this article, has also been the subject of some commentary. *See, e.g.*, *Human Biological Drug Regulation, supra* note 7, at 128-31 (discussing overlap of the FDCA with VSTA and biological provisions of the PHSA). *See also* Peter Barton Hutt and Richard Merrill, Food and Drug Law, Cases and Materials, at 681 (2d ed. 1991); and Gary E. Gammerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 Food & Drug L.J. 213 (1994).

[19] *See, e.g.*, Sec. 645.100, *Biological Drugs for Animal Use* (CPG 7125.14) (explaining overlap of VSTA and the FDCA). *See also* Human Drugs Which Are Biological Products, Redelegated Authority to Administer Certain Provisions of the FDCA, 37 Fed. Reg. 4004 (1972).

[20] *See, e.g.*, Office of Science and Technology Policy, Coordinated Framework for the Regulation of Biotechnology; Announcement of Policy and Notice for Comment, Food and Drug Administration, Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg. 23,302, 23,309-23,313 (1996).

[21] *See, e.g.*, USDA, Bureau of Animal Husbandry, Regulations Governing the Preparation, Sale, Barter, Exchange, Shipment, and Importation of Viruses, Serums, Toxins, and Analogous Products Intended for Use in the Treatment of Domestic Animals (GPO 1907), at 1 (noting that the regulations for the purpose of identification are designated as Bureau of Animal Industry Orders).

[22] *See* Center for Veterinary Biologics, Background and Summary of Activities, *available at* http://www.aphis.usda.gov/vs/cvb/html/background.html.

then renamed the Division of Biologics Standards within the National Institutes of Health; and, ultimately, FDA in 1972.[23]

These organizational changes and their attendant differences can contribute to the sometimes diverse approaches observed in defining biologics. In the early 1900s, Congress could not have anticipated this diversity, particularly in terms of the range and types of products that currently are regulated as biologics, although this is not an unusual feature of legislative enactments.[24] Nevertheless, a number of fundamental legal issues exist that can be associated with the analyses provided here.

These issues include whether either of the agency's actions in describing a product's status as a biologic appropriately comport with relevant legislative intent and statutory language or are *ultra vires*;[25] whether any such actions are entitled to deference in accordance with *Chevron USA, Inc. v. Natural Resources Defense Council, Inc.*, and its progeny;[26] whether agency notices and other informal pronouncements about the status of products as biologics constitute legislative rules that must undergo rulemaking procedures;[27] and whether products that are similar have been treated evenhandedly as biological or nonbiological drugs, both within FDA and APHIS, as well as between the two agencies.[28] Although important, these subjects also are not addressed. The many and varied agency initiatives undertaken over the past one hundred years to characterize as biologics both old and new products would make the presentation especially complex.

III. PRE-1980 HISTORY AND APPLICATIONS OF BIOLOGICS STATUTES AND REGULATIONS

The origins of both the human and veterinary statutes reflect advancements in the late 1800s in the areas of bacteriology and immunology relating to the causation and treatment of human and other animal infectious diseases such as smallpox, measles, diphtheria (whooping cough) and cholera. Experimental animals injected with diphtheria and tetanus toxins were found to produce "antitoxins." In rather simple immunological terms, the toxin, an antigen, which usually is a protein or complex

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[23] *See* Public Health Service and Food and Drug Administration, Statement of Organization, Functions, and Delegations of Authority, 37 Fed. Reg. 12,865 (1972) (noting transfer to the FDA). For a history of organizational changes relating to human biologics regulation, see Ramunas A. Kondaratas, *Biologics Control Act of 1902*, *in* THE EARLY YEARS OF FEDERAL FOOD AND DRUG CONTROL, AMERICAN INSTITUTE OF THE HISTORY OF PHARMACY, at 8 (1982). *See also* Margaret Pittman, *The Regulation of Biological Products, 1902-1970, in* NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE: INTRAMURAL CONTRIBUTIONS, 1887-1997, at 61 (H.R. Greenwald & V.A. Hardin eds., Department of Health and Human Services (1987)).

[24] *See, e.g.,* United States v. Southwestern Cable Co., 392 U.S. 157, 172-73 (1968) (community antenna television systems are subject to regulation even though Congress could not have foreseen their development).

[25] *See generally* Brown & Williamson Tobacco Corp. v. Food and Drug Administration, 153 F.3d 155, 176 (4th Cir. 1998), *aff'd.*, 529 U.S. 120 (2000) (invalidating tobacco regulation).

[26] 467 U.S. 387 (1984) (articulating a two-step process for judicial review of agency interpretations). *See also* United States v. Mead Corporation, 533 U.S. 218, 227 (2001) (noting that *Chevron* deference is applied only when an agency engages in rulemaking or legislativelike procedures that carry the force of law).

[27] *See, e.g.*, Community Nutrition Institute v. Young, 818 F.2d 943 (D.C. Cir. 1987) (FDA action level is a substantive rule requiring notice and comment rulemaking). *But see* Professionals and Patients for Customized Care v. Shalala, 56 F.3d 592 (FDA Compliance Policy Guide was not a substantive rule requiring notice and comment rulemaking).

[28] *See, e.g.,* Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 27 (D.D.C. 1997) (stating an agency must act in a manner that does not result in the disparate treatment of similar products). *See also* United States v. Diapulse Corp., 748 F.2d 56 (2d Cir. 1984).

sugar, called a "carbohydrate," or a combination of both called a "glycoprotein," triggered an immune response to it, namely, typically an antibody (antitoxin).

Serum containing such antitoxins from inoculated animals (usually horses), called "antiserum" or "immune serum," obtained by removing the clotted blood, provided so-called passive immunity to the recipient. The antitoxins or antibodies from the horse reacted with the toxin or antigen to neutralize their biological activity and adverse health effects. Other products, such as vaccines, containing antigens from living, or dead or weakened (attenuated) infectious microbes or parts of microbes, upon inoculation, produced protective antibodies in the recipient, or acquired immunity.

All of these products were rather crude preparations by today's standards. Not surprisingly, therefore, their unregulated marketing eventually led to incidents of contamination. An oft-quoted tragedy that resulted in the enactment of the 1902 legislation governing human biologics relates to a horse named Jim used to produce diphtheria antitoxin. Jim contracted tetanus, resulting in the death of a number of children administered the antitoxin.[29] Upon the subsequent introduction of a bill in Congress to regulate human biologics, it was noted that

> [t]his bill seeks … to regulate the manufacture and sale of certain substances of animal origin which, except vaccine virus, have but recently come into general use for the prevention and cure of disease. The purity of the substance is far more important than the purity of ordinary drugs, because the former are ordinarily injected into the circulation directly while the latter are introduced through the digestive tract.
>
> A dose of an antitoxin, for instance, once administered is beyond recall even immediately after administration; a remedy given by mouth can be removed or neutralized by mechanical means. The potency of these remedies is of corresponding importance … if the first dose proves worthless[,] the loss of time and could cost the life of the patient.[30]

Similarly, veterinary legislation enacted in 1913 was in response to contaminated or worthless products, which resulted in substantial losses by American hog farmers from antihog cholera serum.[31] Testimony indicated that VSTA was necessary to avoid

> dangerous and worthless viruses, serums, and analogous products for use in the treatment of domestic animals, some of which products may be means of introducing disease not now known in the United States, [as well as] be useful [in] controlling the use … of similar dangerous and worthless products that may be manufactured in the United States.[32]

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[29] *See* Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J., 367, 368 (1996). *See also* Pittman, *supra* note 23.

[30] *See* H.R. REP. No. 2713, at 2 (1902).

[31] *See* Hall v. State, 100 Neb. 84, 158 N.W. 362 (Neb. 1916). *See also* Center for Veterinary Biologics, Background and Summary of Activities, *at* www.aphis.usda.gov/vs/cvb/html/background.html.

[32] S. REP. NO. 62-1288, at 2 (1913).

The bill was further explained as important "to protect the farmer and stock raiser from improperly made and prepared serums, toxins, and viruses."[33] Not surprisingly, in light of their similar purposes and legislative histories, the veterinary statute often has been said to be modeled after the human law.[34] Indeed, early legislation covering human and veterinary biologics contained similar definitional language.

A. *Early Statutory and Regulatory Biological Descriptions and Evolution of the "Use" Provisions*

As shown in Table I, the 1902 human statutory provisions simply mentioned any "virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases[35] of man." The 1913 veterinary legislation likewise refers, in relevant part, to any "virus, serum, toxin, or analogous product intended for use in the treatment of domestic animals," language that remains unchanged today.[36]

Because of the similar subject matter of both laws and their comparable legislative histories, and because of the nature of the products that are mentioned, biologics often are said to function by an immune mechanism. As this mechanistic aspect of biological status is also embodied in definitional regulations covering both human and veterinary products, a brief discussion of it is necessary in order to fully appreciate its implications and complexity.

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[33] *Hearing Before the Comm. on Agriculture on the Estimates of Appropriations for the Fiscal Year Ending June 30, 1914 (H.R. 28283)*, 62d Cong., 3d Sess. 24 (1913) (statement of Dr. A.M. Farrington, Asst. Chief, Bureau of Animal Industry, Department of Agriculture).

[34] In hearings pertaining to adoption of the 1913 statute, it was stated that

> [d]uring the House Hearings, Dr. A.M. Farrington, Assistant Chief, Bureau of Animal Industry, explained that the language that is now the Virus-Serum-Toxin Act "follows very closely the law which is now in operation in the United States Public Health Service, where they supervise the manufacture of toxins and viruses for the treatment of human beings."

Estimates of Appropriations for the Fiscal Year Ending June 30, 1914 (H.R. 28283), Hearing Before the Comm. on Agriculture, 62d Cong., 3d Sess. (1913). *See also* Animal Health Institute v. U.S. Department of Agriculture, 487 F. Supp. 376 (D. Co.1980), where the court stated the "Virus-Serum-Toxin Act is properly compared to the 1902 Act because of the similarity of language and of subject matter. In fact, the Virus-Serum-Toxin Act was modeled after the 1902 Act." *Id.* at 378.

[35] There is no APHIS or FDA statutory or regulatory definition of "disease" in a drug-related context except for food health claims, where it is defined in FDA regulations as

> Damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition . . . .

21 C.F.R. § 101.4(a)(5). *See also* DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (28th ed. 1994), defining "disease" as "[a]ny deviation from or interruption of a normal structure or function of any part, organ or system (or a combination thereof) of the body is manifested by characteristics that have symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown, and STEDMAN'S MEDICAL DICTIONARY (25th ed. 1993), defining "disease" as "[a]n interruption, cessation, or disorder of body function, systems, or organs."

[36] The addition of the "antitoxin" and "therapeutic" terminology to the subject matter portion of the human definition does not significantly change its focus. The "analogous products" wordage can cover numerous products, such as antitoxins, particularly since the phrase was undefined. The "therapeutic" addition seems to cover much of the same ground as the "prevention and cure" language. "Therapy" has been defined as "the treatment of disease by various methods," STEDMAN'S MEDICAL DICTIONARY; or as "the treatment of disease," DORLAND'S ILLUSTRATED MEDICAL DICTIONARY. *See also infra* note 42 (defining "treatment").

1. *Basic Immunological Mechanisms*[37]

As alluded to previously, viruses (or other microorganisms such as bacteria) and toxins produced by microorganisms—all can function immunologically as antigens. Such antigens can trigger antibody or other immune responses that are specific to the antigens. In other words, a specific immune mechanism can be triggered, involving antigen-specific antibodies or antigen-specific immunization.

Antibodies or immunoglobulins, which are produced by specialized cells called B-cells, identify a specific antigen. The antibody attachment facilitates destruction or neutralization of the antigen, leading to humoral or antibody mediated immunity (AMI). Another different major type of immunological mechanism is T-cell or cell-mediated immunity (CMI). It can also trigger a specific immune response utilizing certain cells of the immune system to neutralize other cells. Although both cellular and humoral responses can involve antigen-specific mechanisms, a variety of other nonspecific mechanisms also exist that are responsible for generating immunity.

AMI and CMI have historically been considered to play very different roles in providing protection. Antibody responses often occur to circulating pathogens or toxins in the blood such as diphtheria and tetanus toxins, or to pathogens such as polio that multiply outside of cells such as in bodily fluids. Conventional vaccines typically work through AMI. CMI relates more to pathogens that grow or multiply within cells, such as many viruses and the mycobacterium that causes tuberculosis.

Both humoral and cellular immunity function through a series of cascading mechanisms involving a complex variety of other cells and messenger chemicals. The cells include antigen presenting cells, regulatory cells, effector cells, and memory cells. The messengers, which function as intercellular communicators, often are produced or secreted by a cell to affect the activity of another cell. They consist of a vast array of substances called "cytokines," hormone-like[38] molecules that actually can be produced by a variety of immune and nonimmune cells. Cytokines include interleukins, which were originally found to serve as messenger molecules between ("inter") white blood cells called leukocytes ("leukin") and interferons, which "interfere" with viral replication, among other characteristics. Families of cytokines, such as different interferons and interleukins, exist, sometimes named according to their original cell source or function or both.[39]

2. *Human and Veterinary "Subject Matter" Language: 1909 and 1913*

The premise that the original human biologics legislation covered products functioning through an immune mechanism is supported by regulations in existence in 1909. As Table II demonstrates, a number of very specific products are mentioned, such as diphtheria antitoxin, antitetanic serum, antiplague serum

[37] *See generally* JOSEPH A. BELLANTI, IMMUNOLOGY III (W.B. Saunders 1985). *See also* Arturo Casadevall & Liise-anne Pirofski, *A Reappraisal of Humoral Immunity Based on Mechanisms of Antibody-Mediated Protection Against Intracellular Pathogens*, 91 ADVANCES IN IMMUNOLOGY 1 (2006).

[38] *See infra* note 90 and accompanying text.

[39] Tattanahalli L. Nagabhushan & Alexander Giaquinto, *Interferon Alpha-2b: An Overview From a Regulatory Perspective in* REGULATORY PRACTICE FOR BIOPHARMACEUTICAL PRODUCTION 222 (Anthony S. Lubiniecki & Susan A. Vargo eds. 1994) (naming alpha interferon as leukocyte, Type I; beta (fibroblast Type I); and gamma (immune, Type II)). *See also* John Mann, *Lifesaving Drugs, The Elusive Magic Bullet*, ch. 3, *in* ANTIVIRAL TREATMENTS 85, 103 (noting the different classes of interferon, their sources, and functions).

and antituberculosis serum, and a collection of similar "anti" products. These examples clearly evidence the general immunological nature of products covered by the legislation, typically in the form of serum therapies containing antibodies to specific microbial antigens.

The same immunological theme exists with veterinary biologics. In contrast to the human regulatory provisions, however, the nonhuman animal versions were somewhat more elaborative in 1913, as shown in Table III. They defined "analogous products" as including antitoxins and vaccines, as well as "microorganisms, killed microorganisms, and products of microorganisms." The last set of quoted products, referring to "microorganisms," seems to reflect the sources of antigens, namely, "microorganisms." For example, bacteria are microorganisms, and vaccines can be made from killed or attenuated (weakened) bacteria, sometimes called "bacterins"; similarly, a bacterial toxin that is weakened is called a "toxoid."

The reference to "microorganisms" in conjunction with "killed microorganisms" seems redundant unless the first, unqualified terminology was really meant to refer to "living" microorganisms, by way of contrast. This construction seems likely, because the "microorganisms" language was later amended in 1922 to read "living microorganisms," as shown in Table II. The "products of microorganisms" terminology suggests subject matter that is not itself composed of whole microorganisms, perhaps so-called acellular products containing components or other immunizing parts of microorganisms.

The microbial products reference could also have included antibiotics, in theory, which are derived from microorganisms but can also be synthetically derived today.[40] This interpretation is not likely correct, since antibiotics were not used in the treatment of diseases until the 1940s.[41] The language also could have been meant to cover toxins, which often are "produced" by microorganisms. In 1968, however, it was replaced with "the antigenic or immunizing components of micro-organisms," as Table II demonstrates, indicating that the acellular interpretation is correct.

3. *Human and Veterinary "Use" Provisions: 1902-Present*

The other important aspect of the original statutory language relates to "use." The veterinary provision mentions only "treatment," while the human version refers to "prevention and cure of diseases." Whether the term "treatment" was meant to cover "prevention" or "cure," or both, is unclear. Nevertheless, in light of the examples of named products involving serums and vaccines, and given that these products typically involved either the prophylaxis or prevention (vaccines) or cure (serums) of infectious diseases, the "treatment" language of the veterinary provision could have been as broad as the human provision that explicitly mentioned "prevention

[40] An "antibiotic drug" is defined by the FDCA as "any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use containing of any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solutions (including a chemically-synthesized equivalent of any such substance) or any derivative thereof." FDCA § 201(jj), 21 U.S.C. § 321(jj). For a further discussion of the biological status of antibiotics, see *infra* note 58 and accompanying text.

[41] *See Methods of Treatment, Fighting Infection*, at 62 *in* THE EVENTFUL 20TH CENTURY, MILESTONES OF MEDICINE (Reader's Digest Assoc., Inc. 2000).

and cure." Whether such "treatment" language involved diagnosis seems less clear, as a number of medical and other definitions can exist for "treatment."[42]

Whatever the limitations were of the "use" terminology appearing in the early 1900s' legislation, they were ultimately resolved by the mid-1900s. On the human side, the "prevention and cure of diseases" language of the 1902 human biologics statute was revised in 1944 to "prevention, treatment, or cure of diseases or injuries of man," as Table I shows. Regulations promulgated in 1947 added "diagnosis."

One possible reason for the addition of "injuries" was World War II, during which blood and blood derivatives were licensed for transfusion, including whole blood, plasma, and other blood derivatives.[43] The "injury" language still appears in current regulations, although the corresponding statutory language was again altered in 1997 by the FDA Modernization Act (FDAMA).[44] It changed "injuries" to "condition,"[45] as Table I shows. Congressional Reports or debates do not explain this particular revision, except to note the definition "conforms to existing provisions of the law,"[46] which is not quite correct. The term "condition" seems to be broader. It can include injuries as well as other nondisease-related states, such as infertility.[47]

With respect to veterinary biologics, the "subject matter" and "use" provisions of the 1902 statute have not changed; the statute still refers to "treatment." No reference exists to any disease or other condition. Similar to the situation with human biologics, though, the veterinary regulations were eventually updated, in the late 1940s, to define "treatment" as including diagnosis or detection of diseases, as Table III indicates. Later, in 1973, "prevention" terminology was added, although this change seems unnecessary. As discussed before, vaccines, which are explicitly mentioned, are often used preventatively. Still today the veterinary "treatment" terminology covers prevention, diagnosis, management, or cure.[48] The word "management" was added in 1997 when APHIS modernized its definitional regulations for biologics, a topic discussed further below in Part IV. The reasons for this specific addition are again unclear. Given the broad language of the statute involving "treatment," at the time it might have seemed appropriate to expand explicitly the types of veterinary medicinal activities that are covered by the "use" provisions.

Perhaps most important, the current veterinary use provision still does not cover injuries or other nondisease "conditions."[49] This may seem inconsistent with the human provisions, especially in light of the apparently broad "treatment" language of VSTA. Nevertheless, the more restrictive "use" language can make sense, since the "injuries" and "conditions" terminology of the human provisions resulted from *statutory* changes, as noted previously. This fact alone suggests that neither

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[42] *See, e.g.*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (defining "treatment" as "The management and care of a patient for the purpose of combating disease or disorder"); STEDMAN'S MEDICAL DICTIONARY (defining "treatment" as "Medical or surgical management of a patient"); and BLACK'S LAW DICTIONARY, at 1346 (5th ed. 1979) (defining "treatment" as "[a] broad term covering all the steps taken to effect the cure of an injury or disease; including examination and diagnosis as well as application of remedies").

[43] *See* Pittman, *supra* note 23, at 63.

[44] Pub. L. No. 105-115, § 123(d), 111 Stat. 2295, 2324 (1997).

[45] *Id.*

[46] S. REP. No. 104-284, at 80 (1996.)

[47] Pregnancy is not a disease, but a condition. *See* United States v. An Article of Drug—Ova II, 414 F. Supp. 660, 664 (D.N.J. 1975) *aff'd mem.*, 535 F.2d 1248 (3d Cir. 1976).

[48] *See* 9 C.F.R. § 101.2(3).

[49] *Id*. *See also* APHIS, Viruses, Serums, Toxins, and Analogous Products; Definition of Biological Products and Guidelines, Final Rule, 62 Fed. Reg. 31,326 (1997).

statute originally covered nondisease states, which is supported by the history of enactment of both laws relating to infectious diseases.

The practical effect of this more limited use language of the veterinary regulations is significant. Diagnostic tests and other veterinary products for nondisease conditions, such as infertility,[50] can instead be regulated by CVM as non-biological devices or non-biological drugs under the FDCA. This principle, which was alluded to at the outset, is discussed further below, particularly in the context of bovine interferon.

B. *Continuing Evolution of Human Biologics "Subject Matter" Language: 1919-1970*

The types of products that are human biologics changed significantly in 1944 and 1970 as a result of statutory amendments (Table I). Key regulatory changes occurred in 1919, 1923, and 1947 (Table II). Interestingly, all of these major alterations occurred before FDA assumed responsibility for the regulation of human biologics in 1972.

On the veterinary side, important revisions of the regulatory provisions occurred in 1968 and 1997 (Table III). The latter changes are discussed in Part IV, largely because they occurred as a result of advances in immunology and modern biotechnology methods. None are related to any statutory amendments, since VSTA has not been substantively altered in its nearly 100-year history in terms of either its "subject matter" or "use" provisions, as mentioned earlier.

1. *1919 and 1923*

The almost complete change in 1919 of the regulatory subject matter portion of the 1902 human provisions is notable primarily because biologics are described other than by example. Table II shows that the terms "virus," "serum," "toxin," and "antitoxin" are all explained rather simply in basic scientific terms; the last two products, toxins and antitoxins, are particularly described in immunological terms, referring to "specifically neutralizes," "immunized" and "immune." More importantly, an "analogous product" is defined, but incompletely without reference to what it is analogous to, such as to a virus, serum, toxin or antitoxin. Instead, it awkwardly refers either to its source or, for the first time, the product's mechanism of action.

An "analogous product" was one 1) prepared from a virus or other microorganisms "actually or potentially virulent," apparently a reference to the fact that, for example, antigens can be "sourced" or produced from infectious (living) or attenuated microbes, as alluded to earlier, although how a dead microbe can be "potentially virulent" is unclear; 2) prepared or sourced from some constituent of blood; or 3) intended "for specific immunization or therapy." The "some constituent of blood" and "therapy" language both seem to render limitless the nature of substances that can be covered, particularly without the mention of specific products to which the analogous definitions apply.

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[50] In limited preamble language to the revamped final regulations promulgated in 1997, APHIS makes clear that the disease terminology does not include products that control fertility. *See* 62 Fed. Reg. at 31,327. See Part IV. F.

Blood is a suspension composed of red and white cells and a multitude of other constituents or components, often in lesser amounts, such as albumin, amino acids, steroid and other hormones, vitamins, coagulation factors, minerals, and antibodies.[51] Moreover, virtually any type of product presumably can be used as "therapy," since the term was not defined and was used without qualification.[52] The imposition of a mechanism of action requirement involving "specific immunization" is certainly more limiting as well as particularly relevant given the history of biologics. But even this terminology is somewhat unclear, at least in immunological terms, although certain aspects of both CMI and AMI can involve "specific immunization" or perhaps more accurately, a "specific immune mechanism." If such language is read in the context of the named products in the 1909 regulations, some clarity is achieved. Those mentioned are typically serum therapies, toxins, antitoxins or vaccines, which all typically function primarily through AMI or a "specific" antigen-antibody reaction.[53]

Some of the weaknesses of the "analogous product" language in the 1919 regulations were addressed in 1923 (the remaining subject matter language of the 1919 regulations was not significantly altered in 1923). A few of the changes also created new interpretative problems. "Analogous products" were defined again not only in terms of their source or mechanism of action, but also, appropriately, by reference to what they were analogous to, namely, a virus, serum, or toxin and antitoxin. Another improvement was with respect to products analogous to a serum. They were analogous if derived from "some protein constituent of blood," not just any "constituent" of blood. This change makes sense because the immune system can involve many "constituents" that are proteins. One major coverage difficulty with this new language, though, which still exists today, is that many other protein components of blood exist. An array of proteins can therefore have been unintentionally and inappropriately covered, if they are derived from blood. An obvious example is hormones, which typically have their primary effects unrelated to immunological mechanisms, a topic discussed further below.

Additional changes in 1923 related to products analogous to a toxin or antitoxin. Similar to before, such analogues still had a mechanism of action component, involving "specific immunization." "Prevention or treatment" language was also added, even though the wording in the opening of the regulation only referenced "prevention or cure," which seems narrower because "treatment" is probably broader than "cure." Most important, the word "therapy" was dropped, not surprisingly. It had possible unintended broad ramifications as to the types of products that could be covered.

Products analogous to a serum, toxin and antitoxin had to be used parenterally, that is, outside of the digestive track, meaning by nonoral routes of administration, such as injection. This change also is not surprising since immune-based products often must be injected, as alluded to in the legislative history of human biologics, to avoid their destruction in the gastrointestinal tract. On the other hand, analogous products to viruses were not as limited in their route of administration, meaning

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[51] *See generally* ENCYCLOPEDIA BRITANNICA ONLINE, *Composition of Blood*, *at* http://www.britannica.com/ebi/article-197686.

[52] *See supra* note 36 and accompanying text regarding possible definitions for "therapy."

[53] Nonetheless, the other possibility of "specific immunization" involving cellular immunity still exists, too. *See generally* R. Burrell, *Antigen Specific and Antigen Non-Specific Immunization, Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology*, at 77 (Nat'l. Acad. of Sciences 1992). *See also supra* note 37 and *infra* note 122 and accompanying texts.

they could involve oral or any other route of administration. It is not clear whether this difference was purposeful or not, although in 1923 licensed viral vaccines were only administered parenterally, it seems.[54]

Products analogous to viruses or serums did not have to function through "specific immunization" or any immune mechanism, which still is the case today.[55] Nevertheless, again, in light of the types of products licensed at the time, such as toxins, antitoxins, and bacterial and viral antisera,[56] they seemingly would have typically functioned or achieved their preventative or curative effects primarily through an immune mechanism, as discussed earlier. This omission of a mechanism of action requirement, unless it is assumed to be implicitly part of the definitions because of relevant legislative history, means that an abundance of products can be analogous to a virus if prepared "from" a microorganism, such as antibiotics.

This possible anomaly still exists today in light of the literal wording of this human provision, although APHIS altered its biological regulations in 1997 to specifically exclude antibiotics.[57] Nevertheless, antibiotics as a class of products probably were not intended to be regulated as human biological drugs for at least two reasons. They were not used in the treatment of diseases until the 1940s, as noted earlier, and beginning in 1947 they were specifically regulated under their own provision in the FDCA.[58]

2. *1944, 1947, 1961, and 1970*

In 1944, upon reenactment of the biologics provisions as part of the recodification of the PHSA, a very different type of product became subject to biologics regulation, arsphenamine and its derivatives (Table I). The biologics regulations were similarly amended in 1947 to include arsphenical substances (Table II). This class of rather toxic chemicals containing arsenic, one of the first modern chemotherapeutic agents, had been used since 1910 for the treatment of syphilis and certain other diseases.[59] No arsphenamine compounds are apparently currently licensed as biologics, perhaps because treatments for syphilis and other diseases were replaced by much safer antimicrobial compounds, such as penicillin.[60] Certain other arsenic-containing drugs are still medically useful, however.[61] The addition of arsphenamine as a biologic seems to be incongruous with the other named products today, if not in 1944. Why this class of products was not regulated instead under

[54] *See* Pittman, *supra* note 23, at 62-66. The Sabin oral polio vaccine, for example, became available much later in 1957. *See* Neal C. Miller, *The Polio Vaccine: A Critical Assessment of Its Arcane History, Efficacy, and Long-Term Health-Related Consequences*, 1 MEDICAL VERITAS 239, 240 (2004).

[55] *See* 21 C.F.R. § 600.3(h)(5)(i) and (ii).

[56] *See* Pittman, *supra* note 23, at 63.

[57] *See* 9 C.F.R. § 101.2 and *infra* note 207 and accompanying text.

[58] *See* FDCA, § 507, 21 U.S.C. § 357, which was repealed by FDAMA, Pub. L. No. 105-115, 111 Stat. 2296 (codified in scattered sections of 21 U.S.C. and 42 U.S.C.) (FDAMA). *See* FDAMA § 125(b), 111 Stat. 2325-26. It has been said, however, that FDA was persuaded to assume regulatory responsibility for antibiotics and hormones as non-biological drugs, even though they were similar to biologics. *See* John C. Petricciani, *Reinventing the Biologics Approval Process*, 51 FOOD & DRUG L.J. 139, 140 n.7 (1996) (citing a 1970 conversation with Roderic Murray, Director, Division of Biologics Standards, National Institutes of Health).

[59] *See* LEWIS M. MAGNER, A HISTORY OF MEDICINE, at 248 (Marcel Dekker, Inc. 1992).

[60] *Id.* at 349.

[61] For example, arsenic trioxide was approved in 2000 as a new drug for the treatment of patients with a certain type of leukemia. *See* Food and Drug Administration, Talk Paper, FDA Approves Arsenic Trioxide for Leukemia Treatment in Record Time for a Cancer Drug Development Program, No. T00-47 (Sept. 26, 2000), *available at* http://www.fda.gov/bbs/topics/answers/ANS01040.html.

the FDCA[62] is unclear, but could be because they were grandfathered, since they were marketed pre-1938.[63]

The next key changes to the subject matter of the human biologics regulations occurred primarily in 1947. They again related to analogous products, particularly those pertaining to a toxin and antitoxin or to a therapeutic serum. The revisions are important because they still exist today. Some changes also occurred in 1961; a few were relatively minor relating to expanding the definition of a virus (Table II). They simply added the specific names of other types of microbes that were covered, such as fungi and protozoa.

A more significant revision in 1961 involved the mechanism of action aspect of the definition of products analogous to a toxin and antitoxin. The language was changed from "specific immunization" to "a specific immune mechanism." This alteration, which is reflected in current regulations, perhaps is better worded at least from an immunological standpoint. Many mechanisms are involved in achieving immunization, some "specific," others not.

The provision applicable to analogues of a toxin or antitoxin altered in 1947 clarifies its coverage of products "irrespective of [their] source of origin." This source language was possibly added to make clear what was unsaid in the 1923 regulations, namely, that the origin or source of the toxin or antitoxin did not matter. This could have made sense, especially in the context of allergenic products that, as possible analogues of toxins, could be derived from diverse sources such as plants. On the other hand, although allergen testing was practiced in the 1940s,[64] whether any allergenic treatments were actually marketed as biologics in 1947 when the regulations were modified is unclear.[65] Moreover, allergenics were not formally added to the statutory definition until 1970, as discussed below, and it was not until mid-1980 that FDA announced for certain tests licensure as a biologic was required.[66] These considerations, therefore, can suggest that the "irrespective of source" language was not added because of allergenics.

Regardless of the precise reasons for the "source of origin" language, which still exists today, it seems awkwardly worded. If the preposition "of" were changed to the conjunction "or," to read "source or origin," this phrasing would seem to make more sense. If use of the word "of" is a mistake, as it seems to be, it has nonetheless persisted since its adoption in 1947, perhaps because it does not present substantive interpretation problems.

a. *Analogous Products of a Human Therapeutic Serum: Blood and Plasma*

The expansion in 1947 of the types of products that are analogous to a therapeutic serum is significant and worthy of separate attention for a variety of reasons.

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[62] Pub. L. No. 75-17, ch. 675, 52 Stat. 1040 (June 25, 1938).

[63] *See, e.g.*, FDCA, § 201(p)(1), 21 U.S.C. § 321(p)(1), and HUTT & MERRILL, *supra* note 18, at 496.

[64] *See* T. Kim & A. Drake-Lee, Feature Article, *Brief History of Allergy*, 11 ENT. NEWS 1, Nov./Dec. 2002.

[65] *Id.*

[66] "Products used as oral challenges to determine whether persons are allergic to certain chemicals in food, products used adjunctively as positive controls and allergenic skin tests, and chemical reagents used in patch-testing kits are considered biological products subject to licensure." Food and Drug Administration, Allergenic Substances: Policy on Licensure of Oral Products Intended to Determine Allergies, Products Intended as Adjuncts to Allergy Skin Tests, and Materials Intended for Patch Tests of Humans, 51 Fed. Reg. 33,664 (1986). *See also infra* note 81 and accompanying text regarding the statutory amendment in 1970 to cover allergenic products.

For the first time, new classes were included by regulation (arsenicals were added by statutory amendment) that clearly did not necessarily function by any immune mechanism, namely, whole blood or plasma.

The whole blood or plasma language was added as a result of the use of blood transfusions during World War II.[67] The regulation of whole blood and plasma as biologics could have seemed reasonable at the time, because serum had been consistently regulated as a biologic since the initial adoption of biologics legislation in 1902. Further, both serum and plasma are also derived from whole blood. One obvious difficulty with this rationale, however, is the historical context of the original biologics legislation. Serum products were typically used for their immunological properties, as antiserums. This point was not lost on one court that thoughtfully considered the intended scope of the human biologics legislation and regulations.

In *United States v. Blank* [68] the issue was whether whole blood containing citric acid (an anticoagulant) and packed human red blood cells were analogous products to a therapeutic serum. The court ruled they were not, stating

> [n]either … are medically employed for immunological purposes. Their function is to replace blood or blood components which a patient has lost through a disease or injury. Neither of the products described … are prepared from therapeutic serum, and therapeutic serum is not prepared from them. Serum cannot perform the medical functions of either of the described substances, and neither of them performs the functions of therapeutic serum.[69]

It was further noted that blood transfusion was unknown when the biologics legislation was passed in 1902.[70] Although the court acknowledged that the administrative regulations in effect at the time included within their scope whole blood, it nonetheless reasoned that the 1944 revisions to the 1902 statute were minor and not intended to accomplish any substantive changes, other than the addition of arsphenamine and its derivatives.[71]

Perhaps most important, the decision reflects a studied analysis of the considerations that make a product "analogous to a serum," which was defined as "prepared from some protein constituent blood and intended for parenteral administration."[72] The court further noted that, although citrated whole blood and packed human red blood cells are obtained from blood and given by injection,

> [a] common source is a factor of little, if any value in determining whether products are analogous. Blood is a common source of numerous products but that fact sheds little light on whether the products, in the primary sense of analogy, [footnote omitted] have attributes or effects that resemble one another, or in the broader sense of analogy that products are similar or corresponding. Many serums, some fertilizers, beef extracts for human

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[67] *See* Pittman, *supra* note 23, at 63.

[68] 400 F.2d 302 (5th Cir. 1968).

[69] *Id.* at 304.

[70] *Id.* at 303.

[71] *Id.* at 304 n.10. The court also commented that the addition of "injuries" language to the statute in 1944 should not be construed as covering products other than immunological agents because of the same reason that there was no intent to accomplish any substantive changes in the law. *Id.* at 304.

[72] 42 C.F.R. § 22.1 (1938).

> consumption and blood sausage all have their source in blood, but this does not make them analogous. Injection is a meaningful element of analogy but its impact is not great. If it were of much force there would be brought within the ambit of the statute thousands of drugs having not even remote relation or any other attributes to other products named in the statute—anesthetics, vitamins, pollen extracts, and narcotics, to name only a few.[73]

The *Blank* decision created a conflict, because previously in 1962 in *United States v. Calise*,[74] another court held that, citing *United States v. Steinschreiber*,[75] unfractionated (whole) human blood was analogous to a therapeutic serum. In *Steinschreiber*, the circuit court agreed that human blood, whether liquid or dried, is analogous to a therapeutic serum.[76] The district court cited the broad health purposes of the 1902 legislation relating to the sale of certain substances of animal origin and of the importance of their purity.[77] It also recognized that the 1961 implementing regulations (which were similar in substance to the 1947 regulations; see Table II) clearly mentioned analogous products involving blood.[78] Apparently, the district court believed, unlike the court in *Blank*, that the regulations were an appropriate reflection of the subject matter of the Public Health Service Act.

Whatever the merits of the decisions in *Blank*, *Calise,* and *Steinschreiber*, the dispute about the coverage of blood and related products was legislatively resolved in 1970. A statutory amendment was enacted that added "blood, blood component or derivative," as well as "vaccine" and "allergenic product." (Table I) This was the last substantive amendment of the biological subject matter provisions of the PHSA. In enacting the new language, the term "vaccine" was added to make clear that it was covered,[79] although the *Blank* decision did not directly involve vaccines.[80] Also, allergenic products were added because, similar to blood transfusions, they were unknown in 1902 and therefore might also not be considered to be included.[81]

Despite these statutory revisions, parallel changes in the biologics regulations were not made. Apparently this is because whole blood, plasma, and serum are already referenced in the context of therapeutic serum. On the other hand, the current regulations do not contain any explicit mention of vaccines or allergenic products or analogues of them or of analogues of blood products. These omissions may not be of much significance for vaccines. They could be considered analogous to a virus under the current regulations, since they often are composed of viruses or other microbial components. The situation could be very different, however, for allergenics and, particularly, for blood products. A range of other products could be

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[73] 400 F.2d at 305.

[74] 217 F. Supp. 705 (S.D.N.Y. 1962).

[75] 219 F. Supp. 373 (S.D.N.Y. 1963), *aff'd per curium*, 326 F.2d 759 (2d Cir.), *cert. denied*, 376 U.S. 962 (1964).

[76] 219 F. Supp. at 382.

[77] *Id.*

[78] *Id. at* 383.

[79] *See* H.R. REP. No. 191-1035, at 3 (1970) (noting the addition of "vaccine" to the list of covered products is to remove any doubt as to the statute's coverage).

[80] *Id.* at 6 (commenting that the *Blank* decision does not "directly bear on vaccines").

[81] *Id.* A variety of allergenic products are licensed by CBER today. These include insect preparations involving specific house mite types, pollens from a variety of grasses and weeds, and venoms from wasps, hornets, and yellow jackets. *See* Food and Drug Administration, Center for Biologics Evaluation and Research, Current Licensed Establishments and Products, Listed by Product, *at* http://www.fda.gov/cber/ep/part3.htm.

analogous to allergens and blood, blood components, or its derivatives. This point is addressed below in a variety of contexts, especially with regard to the latter set of blood products and certain products of modern biotechnology methods.

b. *Analogous Products of a Human Therapeutic Serum: Organic Constituents*

The remaining significant biologics subject matter added to the 1947 regulations pertained to products analogous to a therapeutic serum "containing some organic constituent or products other than a hormone or an amino acid from whole blood, plasma or serum." The 1923 predecessor provision simply referenced a product prepared from "some protein constituent of blood." This change from a "protein constituent" to "some organic constituent or products" reflects a significant expansion of regulatory coverage, at least for two reasons. Proteins are simply one of many types of organic constituents of blood. Moreover, the "products" language is particularly broad, suggesting that even inorganic components of blood such as minerals are covered.

Despite the broad terminology, a clear attempt was made to restrict the "organic constituent" and "products" coverage to substances that are not hormones or an amino acid. The reason for the "an amino acid" exception is puzzling, although a variety of amino acids are present in blood. Why a single "amino acid" would be excluded, in contrast to, for example, amino acids generally, is difficult to understand. Moreover, amino acids used therapeutically in parenteral nutrition or for other commercial purposes are not derived from blood, but from easily obtainable sources such as by fermentation,[82] so the reason for such a specific exclusion is not evident.

The rationale for the other exception, for hormones, seems clearer. Several types of hormones were already regulated under the 1938 FDCA, such as insulin,[83] which is a protein. It was regulated as a non-biological drug as early as 1941,[84] as were other kinds of hormones, such as conjugated estrogens,[85] which are steroids. Although insulin at the time was primarily obtained by extraction from the pancreas of various animals, and conjugated estrogens are obtained from the urine of horses, this language could have been adopted to make clear that, to the extent other hormones were, or could be, obtained from whole blood, plasma or serum, they also are excluded from regulation as a biological drug.[86]

A possible corollary of the exclusion for hormones is that if the other two analogous product provisions apply, involving viruses or toxins and antitoxins, hormones

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[82] *See, e.g.*, ENCYCLOPEDIA OF AMINO ACIDS: PRODUCTION METHODS OF AMINO ACIDS, *at* http://www.ajinomoto.com/amino/eng/product_print.html.

[83] Insulin is defined to mean "the active principle of the pancreas that affects the metabolism of carbohydrates in the animal body and which is of value in the treatment of diabetes mellitus. The term includes synthetic and biotechnology-derived products that are the same as or similar to, naturally occurring insulin in structure, use, and intended effect and are a value in the treatment of diabetes mellitus." 21 C.F.R. § 200.15.

[84] *See* Insulin Amendments, Pub. L. No. 77-366, ch. 613, 55 Stat. 851, 851-52 (1941). Insulin was specifically regulated under section 506 of the FDCA, 21 U.S.C. § 356. FDAMA repealed the insulin provision resulting in its regulation like other non-biological drugs, similar to antibiotics. *See* FDAMA, § 125(a), 111 Stat. 2325. *See also supra* note 58 and accompanying text.

[85] *See, e.g.*, Food and Drug Administration, Center for Drug Evaluation and Research, Drugs@FDA, FDA Approved Drug Products, Drug Details, listing for Premarin (Brand Name Drug), NDA 004782, original approval date, May 8, 1942, *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

[86] Nevertheless, as explained earlier, it has been said that hormones were purposely regulated as non-biological drugs. *See* Petricciani, *supra* note 58.

perhaps could still be a biologic because such provisions do not explicitly exclude them. As a practical matter, however, this possibility does not seem likely with respect to analogues of toxins and antitoxins, since this provision requires their functioning through "specific immunization." On the other hand, the regulatory coverage of hormones in the case of products analogous to a virus still seems possible. For example, products derived from cells genetically altered by the use of viruses can fall into this analogous product category, as discussed below.[87]

Probably more likely is that all hormones were intended to be excluded from biological status. The singular exclusion for them from analogues of a therapeutic serum could have been justified at the time. No one considered the possibility that hormones could be "prepared with or from" a virus or other microbe, especially since they were often obtained by extraction from nonhuman animal sources or made synthetically.[88] Nor did anyone probably think they could function by a "specific immunization" or any immune mechanism. In other words, it seems likely that the solitary exclusion for hormones in the analogous product provisions is not a drafting error, but purposeful.

Another aspect of the exclusion for hormones is defining what they are, as there is no description in FDA's laws or regulations.[89] Moreover, since the late 1940s when the hormone language was added, advances in endocrinology, as well as in immunology and other scientific disciplines, have made the topic much more complicated. For example, explaining the differences and similarities between hormones and other substances such as cytokines, which have some characteristics that are similar to hormones and vice versa, can be challenging. This fact explains why cytokines often are described as "hormone-like."[90]

3. *Other Human "Subject Matter" Developments*

A few other definitional-related topics worthy of mention occurred primarily in the 1970s or early 1980s. In 1973, FDA announced the biological status of a preparation of circulating blood cells (amebocytes) of the horseshoe crab (*Limulus polyphemus*) used in detecting bacterial endotoxins in biological products and other drugs for parenteral administration.[91] It cited applicable regulations at the time that defined a biological product as a virus, therapeutic serum, toxin, antitoxin, or analogous product used for diagnosis.[92] The biological status of the "LAL test," as it became known, is not surprising since the crab blood amebocytes contain a

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[87] Erythropoietin is a glycoprotein hormone approved for a variety of indications involving anemia. Synthesized primarily by the kidney, it circulates in the plasma and acts to stimulate cells in the bone marrow to produce red blood cells. *See* A. Engert, *Recombinant Human Erythropoietin in Oncology: Current Status and Further Developments*, 16 ANNALS OF ONCOLOGY 1584 (2005). Why it is regulated as a biologic is unclear in light of its hormone status, but its derivation utilizing recombinant cellular and viral sequences could be at least one reason. *See also infra* note 117 and accompanying text.

[88] *See* Yuan-yuan H. Chiu, *Recombinant Peptide Hormones*, *supra* note 39, at 330.

[89] *See* A. Turnbull & C. Rivier, *Regulation of the Hypothalamic-Pituitary-Adrenal Axis By Cytokines: Actions and Mechanisms of Action*, 79 Physiol. Rev. 2, 2 (1999) (defining a hormone as 'a biomolecule, which is produced by a specialized cell type, is secreted from a ductless gland directly into the blood stream and acts on distant cells/tissues, to regulate preexisting cellular activities').

[90] *See id.* and Yuan-yuan H. Chiu, *Recombinant Peptide Hormones*, *supra* note 39, at 330.

[91] Food and Drug Administration, Status of Biological Substances Used for Detecting Bacterial Endotoxins, 38 Fed. Reg. 1404 (1973).

[92] 21 C.F.R. § 273.101(i) and (k) (1973).

clotting factor, which attaches to endotoxins.[93] The amebocytes, therefore, could be considered analogous to a therapeutic serum or to antitoxins.

A different decision by FDA pertains to the biological status of plant seed extracts called "lectins," which are products that have carbohydrate-binding capabilities. Lectins can be used as alternate sources to human sera for blood typing. If used for such purposes they are *in vitro* diagnostic products that are not biologics, according to FDA.[94] This position is not surprising in the sense that lectins are not derived from blood, plasma, or serum or from microbes. Nevertheless, they can be toxins[95] or perhaps could be analogous to allergenic products, which can be derived from plant, insect and other diverse sources.

A few other decisions that are clearly consistent with the definitions for a human biologic include that in *Certified Blood Donor Services v. United States.*[96] Here the court held that for purposes of tariff schedules, which were based on the biological definitions established by FDA, imported diagnostic serum was a biologic. Similarly, in *United States v. Miami Serpentarium Laboratories, Inc.*,[97] the court held that a mixture of whole snake venom and snake venom fractions were a biological product. FDA has also stated that a product called "immune milk" for the treatment of various diseases such as rheumatoid arthritis is a biologic because it is made of bacterial antigens.[98]

4. *Veterinary Biologics Regulatory "Subject Matter": 1968*

The changes in the subject matter provisions of the 1968 regulations, in contrast to those described above for human biologics, present a very simple evolutionary analysis until the advent of modern biotechnology in the early 1980s. Although substantive subject matter changes occurred in 1973 (Table III), they were not that significant and, therefore, will not be discussed.

The theme of the 1968 regulations (Table III), similar to their human counterparts, is one involving the immunological nature of biologics, as alluded to above. They mentioned viruses, serums, toxins and analogous products, such as antitoxins, vaccines, live microorganisms, killed microorganisms and the "antigenic or immunizing components" of microorganisms. The added language, "antigenic or immunizing components," also specifically emphasizes that acellular products can be biologics, as is the case with human products. More important, unlike the human regulations, the veterinary versions covered products of natural or synthetic origin. This coverage exists yet today.

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[93] A number of LAL products have been licensed. *See* Food and Drug Administration, Current Licensed Establishment and Products, Listed by Product, *at* www.fda.gov/cber/ep/part3.htm. FDA has a guideline on LAL testing. *See* CDER, CBER, CDRH, CVM, Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices (Dec. 1987).

[94] Food and Drug Administration, Additional Standards for Diagnostic Substances or Laboratory Tests, Blood Grouping Sera, 42 Fed. Reg. 54,534, 54,535 (1977).

[95] *See, e.g.,* Food and Drug Administration, Center for Food Safety and Applied Nutrition, Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, Phytohaemagglutinin, *at* www.cfsan.fda.gov/~mow/chap43.html. *See generally* Els. J.M. Van Damme et al., HANDBOOK OF PLANT LECTINS: PROPERTIES AND BIOMEDICAL APPLICATIONS (Wiley 1998).

[96] 511 F. 2d 572 (C.C.P.A. 1975).

[97] Food, Drug, Cosm. L. Rep. (CCH) [1982-83] Dev. Trans. Binder ¶38,164 (S.D. Fla. 1982).

[98] *See* Food and Drug Administration Compliance Guide, § 275.100, CPG No. 7134.04 (Mar. 1995).

IV. BIOLOGICS AND THE KEY DEVELOPMENTS OF THE MODERN BIOTECHNOLOGY ERA

With the modern biotechnology revolution in the early 1980s heralding a wave of new products, such as interferon, erythropoietin and monoclonal antibodies, a number of developments were prompted involving CBER. These included its initial reorganization into discrete review divisions oriented toward certain types of products[99] and, more recently, the transfer of many therapeutic biologics to CDER.[100] Particularly relevant to this paper are early statements about the regulation as biologics of modern biotechnology products and how these statements evolved as new products emerged. FDA initially said modern biotechnology products would be handled on a case-by-case basis.[101] Some of its other early initiatives regarding biologics were typically in the form of "Points to Consider" documents and other guidances. These initiatives address a number of diverse topics, such as those pertaining to the manufacturing and testing of monoclonal antibodies and interferon.[102]

With a few notable exceptions,[103] this trend continues yet today. FDA continues to issue informal, nonbinding guidances and other statements, seemingly often reflecting policy or interpretative positions.[104] This informality in its approach to the regulation of modern biotechnology products has carried over to matters concerning their biological status. In fact, the human biological regulations were last substantively amended in 1947 and long before FDA assumed responsibility for

[99] *See* Food and Drug Administration; Statement of Organization, Functions and Delegations of Authority, 57 Fed. Reg. 54,241 (1992). *See also* Kathryn C. Zoon, *Initiatives and the New Structure at the Center for Biologics Evaluation and Research*, 6 REG. AFF. 201 (1994); *CBER Restructuring Proposal Would Create New Offices For Vaccines, Blood Products, And Licensing: Three Associate Center Directors To Be Added*, Food, Drug, Cosm. Rep. ("The Pink Sheet"), June 1, 1992, at 7.

[100] Food and Drug Administration, Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research, *at* http://www.fda.gov/oc/combination/transfer.html and U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Therapeutic Biological Products, *at* http://www.fda.gov/cder/biologics/default.htm. *See also* Food and Drug Administration, Drug and Biological Product Consolidation, 68 Fed. Reg. 38027 (2003). For a list of transferred products, see Food and Drug Administration, Center for Biologics Evaluation and Research, Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, Approved Products Transferring to CDER, *at* http://www.fda.gov/cber/transfer/transfprods.htm.

CBER is still responsible for handling a number of non-biological drugs approved under the FDCA that are anti-coagulants involving chemicals such as citrate and plasma volume expanders for the treatment of shock containing, for example, dextran and hetastarch. *See* U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF PHARMACEUTICAL SCIENCE, OFFICE OF GENERIC DRUGS, DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATION (27th ed. 2007), Drug Products With Approval Under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research List, *available at* http://www.fda.gov/cder/orange/505.htm.

[101] Food and Drug Administration, Statement of Policy for Regulating Biotechnology Products, 49 Fed. Reg. 5878, 5878 (1984).

[102] *See, e.g.*, Food and Drug Administration, Biological Products; In Vitro or In Vivo Monoclonal Antibodies, Products Made Using Recombinant DNA Technology, or Interferon; Availability of Draft Criteria for New Technologies; Request for Comments, Data, and Recommendations, 49 Fed. Reg. 1138 (1984) (announcing availability of documents pertaining to monoclonal antibodies, recombinant DNA biological products, and interferon).

[103] *See, e.g.,* Elimination of Establishment License Application [ELA] for Specified Biotechnology and Specified Synthetic Biological Products, 61 Fed. Reg. 24,227 (1996) (codified in relevant part at 21 C.F.R. § 601.2(a)-(c)). The ELA requirement was eventually eliminated by FDAMA. *See supra* note 13 and accompanying text.

[104] *See, e.g.*, Food and Drug Administration, Interim Definition and Elimination of Lot-By-Lot Release of Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products, 60 Fed. Reg. 63,048 (1995).

biologics regulation in 1972, as noted earlier.[105] This is in stark contrast to APHIS, which has promulgated rules effecting substantive changes in its definitions of a veterinary biologic to reflect modern biotechnology advancements and other developments, as discussed below.[106]

One of FDA's earliest efforts to address informally the scope of its biologics jurisdiction was in 1983, when it promulgated a notice stating that all monoclonal antibodies were biologics.[107] This was not surprising since such products are composed of antibodies. Another early product, however, recombinant interferon, prompted significant regulatory debate,[108] including about its possible status as a biologic. Other new biotechnology products or product classes whose classification by FDA became benchmarks of its biologics jurisdiction are each discussed separately below. These include gene and cellular therapies, tissue products, and cloning.

A. *Early Interferon Debate*

The controversy began in 1982 when FDA and APHIS published a Memorandum of Understanding (MOU) pertaining to the responsibilities of each agency for regulating nonhuman animal products as biologics under VSTA instead of as drugs under the FDCA.[109] The MOU states that

> [v]eterinary biologics include bacterins, sera, antisera, antitoxins, toxoids, allergens, diagnostics, antigens prepared from or derived from microorganisms or products of microorganisms, animal tissues, animal fluids, or other substances of natural or synthetic origin.

APHIS further comments in the MOU that "Animal biological products generally act through a specific immune process."[110] This was a particularly curious statement because applicable APHIS regulations contained no such language (Table III), nor does VSTA. In fact, this mechanistic aspect seems to have been borrowed from the human regulations governing products analogous to a toxin or antitoxin.

Comments on this fundamental jurisdictional issue raised by the MOU therefore questioned its legality.[111] In response, USDA admitted that nothing in its current regulations or in VSTA restricted its jurisdiction to products acting solely in this manner, explaining, therefore, that the reference to "specific immune process" was qualified by use of the word "generally." Despite these acknowledgments, recombinant bovine interferon is regulated as a drug under the FDCA because it

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[105] *See* Part III. B.

[106] *See infra* Part IV.F.

[107] *See* Food and Drug Administration, Licensing of a Biological Monoclonal Antibody Product Prepared by Hybridoma Technology, 48 Fed. Reg. 50,795 (1983).

[108] Human interferon produced naturally or through genetic engineering techniques is a biological drug, according to FDA. *See, e.g.*, Food and Drug Administration, Interstate Shipment of Interferon for Investigational Use in Laboratory Research Animals or Tests In Vitro, Notice, 48 Fed. Reg. 52644 (1983) (advising that widespread media attention to interferon as a miracle cure necessitates the issuance of a reminder about the investigational biological drug due diligence requirements to ensure that interferon laboratory research uses are not diverted to human uses).

[109] Memorandum of Understanding with the United States Department of Agriculture, Animal and Plant Health Inspection Service, Food and Drug Administration, 47 Fed. Reg. 26458, 26459 (1982).

[110] *Id.*

[111] Department of Agriculture, Final Policy Statement for Research and Regulation of Biotechnology Process and Products, 51 Fed. Reg. 23,302, 23,346 (1986).

does not function through a "specific immune process." In contrast, recombinant human interferons, among other cytokines, are regulated as biologics under the PHSA.[112]

This difference can be analyzed in a variety of ways. With respect to bovine interferon, the science seems to be right, but the regulatory conclusion about its non-biological status appears to be wrong. A technical complexity in addressing this topic is that "interferon" is actually a class of proteins that can function in a variety of ways, not always involving an immune mechanism, as alluded to in the section on basic immunology. The bovine interferon at issue was of the type that did not function primarily by an immune mechanism. On the other hand, from a legal standpoint, no veterinary biologics definitional regulations in the 1980s referenced any mechanism of action, even though the history of VSTA suggests that products that function immunologically can be biologics. The result is that bovine interferon should have been treated as a biologic similarly to human interferons, it seems, at least at the time.

The biological status of human interferons can be assessed primarily in terms of how they are derived or "sourced," from either an experimental or commercial standpoint. Often, however, experimental methods were not useful for commercial production at least until the development of recombinant DNA methods.[113] An example is tissue plasminogen activator, licensed in 1987 as a thrombolytic (blood clot dissolving agent).[114]

Experimentally, different types of human interferons have been produced in various ways, including by stimulating or inducing certain types of blood cells or other cells with antigens such as viruses, or viral or bacterial components, or even chemicals.[115] Interferons from blood cells such as lymphoblasts (interferon gamma) or from leukocytes (interferon alpha)[116] could therefore be considered to be products analogous to a therapeutic serum. They are "some organic constituent" or "product" other than a hormone or an amino acid. Such products might also be considered analogous to a virus because, although they may not be prepared "from" a virus, they could be viewed as prepared "with" a virus or other similar agent.

The commercial production of interferons can present a similar definitional analysis. They typically are produced using recombinant DNA methods involving cells or so-called cell substrates containing the gene responsible for the particular interferon. The gene is inserted in the cells through the use of viral or other microbial vectors. The cell substrates do not usually involve blood cells, but a variety of other cells, such as yeast and *E. coli*, which can serve as suitable microbial production

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[112] *See, e.g.*, Food and Drug Administration, Center for Drug Evaluation and Research, Drugs@FDA, listing for "Interferon" (showing 11 licensed interferons) *at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

[113] Tattanahalli L. Nagabhushan & Alexander Giaquinto, *Interferon Alpha-2b: An Overview From a Regulatory Perspective, supra* note 39, at 223, (stating that "availability of interferon from natural sources and the amounts and purity needed for controlled clinical trials was essentially nonexistent even two decades after its discovery in 1957"). *See also* Roche Facets, *Pegasys Improves Things For Patients With Chronic Hepatitis C, Bacteria Can Produce Single Products* (noting that it takes sixty thousand liters of human blood in order to produce one gram of interferon), *at* http://www.roche.com/pages/facets/10/pegasyse.htm.

[114] Deborah Beebe & Genesio Murano, *Tissue Plasminogen Activator: Regulatory Issues*, *supra* note 39, at 282. *See also* Food and Drug Administration News, TPA Approval—Blood Clot Dissolver, No. 87-32 (11/13/1987). For a discussion of thrombolytic product regulation, see *infra* note 131 and accompanying text.

[115] Tattanahalli L. Nagabhushan & Alexander Giaquinto, *Interferon Alpha-2b: An Overview From a Regulatory Perspective, supra* note 39, at 222.

[116] *See supra* note 39 and accompanying text.

factories.[117] Because of these source differences, though, in the case of applying the provisions applicable to a product analogous to a therapeutic serum, the "organic constituent or product," interferon, is not derived from whole blood, plasma, or serum. Alternatively, it might more appropriately be considered analogous to a virus, as above in the case of experimental sources, because of the use of viral or other similar agents in its preparation by recombinant DNA methods. Then, too, the analogous product provisions applying to a toxin or antitoxin could be relevant, but only if the type of interferon functions through "a specific immune mechanism," not an immune mechanism more generally.

A possible interpretative problem exists with applying in this manner the toxin and antitoxin and other analogous provisions. Products could be covered that are very different from those they are supposed to be analogues of, namely, a virus, serum, or toxin, or antitoxin. As suggested in *Blank*, albeit in a slightly different context, an analogous product could therefore not have any remote relation to any of the attributes of the products named in the statute.[118]

In terms of statutory interpretation, the following canons of *noscitur a sociis* and *ejusdem generis* could require a more restricted approach: where general words (e.g., "analogous products") follow the enumeration of a specific class of things (e.g., "virus, serum, toxin, or antitoxin"), the general words should be construed as only referring to that class; no broader construction should be allowed.[119] In the interferon examples, this could mean that the analogous product provisions should be read in conjunction with, in particular, the regulatory definitions of a virus, toxin, or antitoxin. If so, the analogous product provisions would likely be much more limited in their coverage.

B. *FDA Intercenter Agreements*

In 1991 FDA published a number of intercenter agreements describing product characteristics or product types and their status as biological or non-biological drugs or devices, or as combination products.[120] Although the precise statutory or regulatory bases for the assignments are not always addressed, and the agreements are dated or have been superseded in some respects,[121] they nonetheless are still instructive. For the first time FDA seems to identify categories or classes of products that are biologics, revealing some interesting differences in regulatory treatment. Moreover, the agreements seem to have inspired later statements or positions by FDA on the biological status of certain modern biotechnology products, particularly those from cells altered by recombinant DNA methods. The agreement between CBER and CDER is particularly relevant here.

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[117] *See* Anthony S. Lubiniecki & Susan A. Vargo, *Introduction to Regulatory Practice in Novel Biotechnology, supra* note 39, at 4-8 (listing a variety of cell substrates).

[118] *See* 400 F.2d at 305.

[119] *See, e.g.*, Washington Dep't. of Social and Health Service v. Guardianship Estate of Danny Keffeler, 537 U.S. 371, 384 (2003) (citing other cases, noting that "Words are known by their companions" and the maximum *noscitur a sociis* is applied where a word is capable of many meanings in order to avoid giving unintended breadth to legislation.).

[120] *See generally* Food and Drug Administration, Assignment of Agency Component for Review of Premarket Applications; Guidance Documents Entitled Intercenter Agreements for Biologic, Device and Drug Products; Availability, 56 Fed. Reg. 58760 (1991) (announcing the availability of the Intercenter Agreements).

[121] *See* Food and Drug Administration, Jurisdictional Update: Intercenter Agreements, *at* http://www.fda.gov/oc/combination/intercenterupdate.html.

CBER and CDER are each responsible for a number of product types that are recognizable as biological or non-biological drugs, largely because of their nature or source, or both. CBER handles vaccines[122] and allergenic products, regardless of their method of manufacture. It also is responsible for human blood or human blood-derived products, including placental blood-derived products; animal or cell-culture-derived hemoglobin-based products intended to act as red blood cell substitutes; immunoglobulin (antibody) products, produced in human beings, animals, or in cell cultures; and animal venoms (toxins) or constituents thereof.

Also as expected, CDER is responsible for antibiotics and hormone products, regardless of their method of manufacture or source. It further is assigned naturally occurring substances purified from mineral or plant source materials, unless they are vaccines or allergenics. These latter CDER categories and their biological exceptions can make sense. Vaccines and allergenics are obviously biologics, regardless of their sources. Medicines such as paclitaxel, obtained semi-synthetically from the Pacific Yew tree and used as an anticancer agent, is clearly a non-biological drug in terms of its source and mechanism of action involving the inhibition of cancer cell division.[123]

On the other hand, if a product were plant-derived, it could seemingly still qualify as a human or veterinary biologic. An applicable human regulatory provision could be that pertaining to analogues of a toxin or antitoxin, if the product acts through a specific immune mechanism. Alternatively, the human statutory provision pertaining to products analogous to allergenics could apply. Neither of these definitional options involves a source requirement. The veterinary side is easier to address if an immune process is involved, a topic discussed further below in more detail. Indeed, APHIS has already licensed such a plant product, acemannan,[124] an aloe-derived polysaccharide for use as an immunostimulant.[125]

One of the most noteworthy CDER assignments pertains to products that are chemically synthesized or synthetic. Such substances, excluding vaccines and allergenics for some reason, are regulated as non-biological drugs, even when, for example, they are analogues of cytokines, thrombolytics, or other biologics. The exception for allergenics and vaccines, unlike before, is curious. It seems difficult to justify for these two classes of products and not for others, especially because how products are derived or sourced are not always deciding factors of human biological status. If a product were analogous to a toxin and antitoxin because it functions through a specific immune process, it is a biologic whether or not it is synthetic. Also, such a categorical interpretation that chemical or other "non-natural" sources always affect the status of a product as a human biologic is inconsistent with the current veterinary provisions. They provide that chemical synthesis or synthetic

[122] Interestingly, a vaccine is not defined generally in terms of evoking an immune response, but as "an agent administered for the purpose of eliciting an antigen-specific cellular or humoral immune response to it." Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation Research, *supra* note 121, at III.B.1.a.

[123] *See* Food and Drug Administration, Center for Drug Evaluation and Research, Drugs@FDA, listing for Taxol, Label and Approval History, Label Information, *at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[124] *See* USDA, Veterinary Biological Products, Licenses and Permittees (Dec. 2006), at 93, *available at* http://www.aphis.usda.gov/vs/cvb/RegsGuidance/CurrentProdCodeBook.pdf (listing for "acemannan" as an "immunostimulant").

[125] *See, e.g.*, J.K. Lee et al., *Acemannan purified from aloe vera induces phenotypic and functional maturation of immature dendritic cells*, 1 INT. IMMUNOPHARMACOL. 1275 (2001).

origin do not affect biological status, provided an immunological mechanism is involved.[126]

Another interesting category of non-biological drug products are specific classes of substances produced by fungi or bacteria. These include disaccharidase and HMG-Coenzyme A (CoA) reductase inhibitors,[127] and certain products derived from human or other animal tissue.[128] The referenced inhibitors prevent certain bodily enzymes from working in sugar metabolism or cholesterol synthesis. Disaccharidase inhibitors and similar substances include acarbose that is involved in the management of Type 2 diabetes and is fermentation-derived.[129] The HMG-CoA reductase inhibitors encompass a wide array of "statins," used for treatment of hyperlipidemia, or hypercholesteolemia, such as atorvastatin and lovastatin.[130] As a class, these substances can be fermentation- or synthetically-derived. They are all regulated as non-biological drugs, even though some can be obtained from cellular sources involving bacteria, for example. In terms of their biological status, they could be considered products analogous to a virus. They are produced "with" the use of a virus or other agent (bacteria), in accordance with 21 C.F.R. § 600.3(h)(5)(i) (Table II).

Other classes or types of products are regulated as biological drugs, despite being similarly derived or sourced. Thrombolytics, such as streptokinase[131] and reteplase,[132] which can also be derived from sources such as bacteria or cells altered by recombinant DNA methods, are mainly regulated as biological drugs. This status of thrombolytics, however, becomes slightly more complicated because of urokinase. Originally derived from urine[133] and then later from neonatal kidney cells in tissue culture,[134] it is regulated as a non-biological drug, as are two other very different types of enzyme products that are structurally similar and used for the treatment of Gaucher's disease: alglucerase, which is commercially obtained from human placenta tissue, [135] and imiglucerase, produced by recombinant DNA methods. [136]

The reasons why these sets of different products, which are secreted by or extracted from cells or tissues, are not all treated as biological drugs are uncertain. One possibility is that those that are fermentation-derived could have been viewed as similar to antibiotics, which also are often obtained in this manner. Likewise,

[126] *See* 9 C.F.R. § 101.2 and Table III. *See also infra* note 209 and accompanying text.

[127] *See* CDER-CBER Intercenter Agreement, *supra* note 121, at III.A.4.

[128] *Id.* at III.B.1.f.

[129] *See* PHYSICIANS' DESK REFERENCE (61st ed., 2007), at 751 (listing for Precose® (acarbose) describes it as an oral alpha-glucosidase inhibitor for the management of Type II diabetes mellitus composed of an oligosaccharide obtained from the fermentation of the bacterial microorganism *Actinoplames utahensis*).

[130] *Id.* at 2483 (describing Lipitor® (atorvastatin calcium) as a synthetic lipid lowering agent) and 2021 (describing Mevacor® (lovastatin) as a cholesterol lowering agent isolated from a strain of *Aspergillus terreus*).

[131] *See Physicians' Desk Reference* (44th ed. 1990), at 1048 (listing for Streptase® (streptokinase) describes it as a bacterial protein elaborated by a Group C beta-hemolytic streptococci).

[132] *See Physicians' Desk Reference* (61st ed. 2007), at 2499 (listing for Retavase® (reteplase) describing it as produced by recombinant DNA technology in *E. coli*).

[133] Joseph C. Fratantoni & Kenneth B. Seamon, *Evaluation of Recombinant Human Erythropoietin as a Therapeutic Agent*, *supra* note 39, at 299.

[134] *See Physicians' Desk Reference* (58th ed. 2004), at 407 (listing for Abbokinase® (urokinase) describes it as obtained from human neonatal kidney cells grown in tissue culture).

[135] *See Physicians' Desk Reference* (49th ed. 1995), at 1090 (listing for Ceredase® (alglucerase) describes it as a modified form of beta-glucocerebrosidase purified from a large pool of human placental tissue from selected donors).

[136] *See Physicians' Desk Reference* (61st ed. 2007), at 1270 (listing for Cerezyme® (imiglucerase) describes it as an analogue of the human enzyme beta-glucocerebrosidase, produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary)).

products from tissue or urine could have been considered to be similar to hormones that historically were sometimes also produced from these sources. A further, perhaps more important, explanation for the differences relates to ensuring regulatory consistency. Whatever the initial reasons were for members of a product class or type being treated as biological or non-biological drugs, they were handled the same once their source or method of manufacture changed.[137]

While such consistency is clearly important, these types of examples and others not addressed here are problematic. They represent a few of the many reasons why a maze exists today in classifying and regulating human drug products as biologics. While the source aspects of the human biological provisions are at the core of the inconsistencies associated with these examples, so are the other multiple, diverse criteria that plague understanding the human definitions more generally.

Other products listed in the intercenter agreement as subject to CBER jurisdiction include those that are protein- or cellular-based:

> Products composed of or intended to contain intact cells or intact microorganisms, including bacteria, fungi, viruses … or viral vectors;
>
> Protein, peptide or carbohydrate products produced by cell culture, excepting antibiotics and hormones … and
>
> Protein products produced in animal body fluids by genetic alteration of the animal, i.e., transgenic animals.

The bases for the biological status of each of these three broad classes of products is not stated. They can be explained in some cases or not in others, as before.

1. *Intact Microorganisms, Intact Cells, and Viral Vectors*

Products composed of intact microorganisms, such as bacteria and fungi, or viral vectors composed of nucleic acid (DNA or RNA) sequences, are probably easily classified as "analogous to a virus." In terms of the relevant regulatory language, they are prepared "with" a virus or agent actually or potentially infectious, or at least without regard to the virulence of the strain utilized.[138]

The biological status of "intact cells" seems more difficult to explain. Coverage exists under the analogous product provisions of section 600.3(h)(5), if the cells are, in most relevant part, 1) prepared from or with a virus; 2) derived from whole blood, plasma, or serum; or 3) applicable to the treatment of disease through a "specific immune process." Although any one or more of these criteria could apply under appropriate circumstances, particularly the first two, none is necessarily applicable across the board to all cells. A few possibilities are discussed in more detail below in the next section.

One other option for regulating as biologics "intact cells" that otherwise do not meet the regulatory definitions of analogues is the statute itself. The provisions involving products analogous to "blood, blood components, or derivatives" are

[137] This very point is mentioned in the CDER-CBER Intercenter Agreement, *supra* note 121, at III.C.2 (stating that new products using the same active ingredients as approved products will be regulated by the same biological or non-biological mechanism as the approved products).

[138] As early as 1986, FDA stated that nucleic acids or viruses used for gene therapy are biological drugs. Food and Drug Administration, Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg. 23,309, 23,311 (1986).

pertinent, although, as mentioned previously, no regulations cover such analogues. The absence of regulations in this area can make this type of analysis more difficult or easy, depending on one's perspective.

Since blood contains, mostly, red and different types of white cells, "intact cells" arguably could be "analogous" to any one of them. Indeed, whole blood transfusion in some respects is cellular therapy, although many types of cells exist in the body having characteristics and functions very different from blood cells. Examples include pancreatic, liver, reproductive (i.e., sperm and egg), kidney, and neural cells, among others. These have little in common with blood or with immunological-based treatments more generally.

2. *Cell Culture Products*

The second category of products assigned to CBER — protein, peptide, or carbohydrate products produced by cell culture — also seems too broad, unless the cells are from blood. The coverage appears to be aimed at those substances derived from the use of recombinant DNA methods, which can involve many different types of cells that have nothing to do with blood, as described earlier. As with the previous analysis regarding the biological status of "intact cells," the products here, proteins, peptides and carbohydrates, can also pose challenging interpretative issues. The key difference now, though, is that the products are not cells themselves, but produced by cells.

Two analogous product provisions could apply. One is again the subsection covering toxins and antitoxins, if the products function through a specific immune process. Not all substances produced by recombinant or other methods involving cell substrates, however, such as certain interferons and tissue plasminogen activator,[139] function by an immune process, specific or otherwise. Another analogous product provision that therefore could apply pertains to viruses or other similar agents. Proteins or carbohydrates can be prepared "with" a virus or other microbial agent, since the cells that are utilized often are genetically altered with viral or other microbial sequences. This point was addressed above in the context of interferons.

With respect to the product exclusions for antibiotics and hormones, they make sense, as discussed earlier, although antibiotics have yet to be formally excluded by regulation. Hormones, on the other hand, are already excluded, albeit perhaps not generally but only as part of the analogous product language pertaining to a therapeutic serum, as also mentioned previously.

3. *Transgenic Animal Products*

The last category of biological products is human proteins produced in transgenic nonhuman animal body fluids.[140] Human monoclonal antibodies manufactured in

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[139] *See supra* notes 114-117 and 131 and accompanying text.

[140] A transgenic animal can be loosely defined as one that contains foreign genes or genetic information, i.e., from another organism. *See, e.g.,* BIO 2005-2006 Guide to Biotechnology, at 149, *at* www.bio.org/speeches/pubs/er/BiotechGuide.pdf.

FDA has promulgated guidances on the use of transgenic animals and plants to produce pharmaceuticals. *See, e.g.*, Food and Drug Administration, Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived From Transgenic Animals, 60 Fed. Reg. 44,036 (1995) (announcing availability). *See also* HHS, FDA, CBER, CDER, CFSAN, CDRH, CVM, USDA, APHIS, Center for Veterinary Biologics, and Biotechnology Regulatory Services, Guidance for Industry, Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals, Draft Guidance (2002).

goats, for example, could easily fit into this category, given their status as antibodies. Again, though, the category is overly broad. For example, the protein could be a human hormone produced in milk, not a product or a fluid source necessarily triggering biological status. A more complex topic is the biological status of products used to engineer such transgenic nonhuman animals, discussed in the section on veterinary biological and nonbiological drugs.

C. *Human Somatic Cell and Gene Therapy Products, and HCT/Ps*

The first human gene therapy experiment using a viral vector was approved in 1990.[141] Such experiments were originally handled by the National Institutes of Health (NIH) Recombinant DNA Advisory Committee,[142] although this type of work eventually led to FDA regulation. The oversight of gene therapy experiments by NIH and FDA and the history of such therapy are discussed extensively elsewhere.[143] Gene therapy also became part of so-called somatic cell therapy, which involves a variety of different somatic (nonreproductive) cells that are genetically modified. Somatic cell therapy can further entail cells that are otherwise changed in their characteristics to provide therapeutic value. Both human gene and somatic cell therapy are intended to effect nonheritable changes not involving the germ line or sex cells, such as sperm and eggs.

The status of such cellular and gene products was addressed by FDA in a notice promulgated in 1993.[144] It states that such cells are biological drugs subject to regulation under the PHSA and the FDCA.[145] The agency defines somatic cell therapy as involving the administration of autologous (self), allogeneic (intraspecies) or xenogeneic (interspecies) cells that are manipulated or altered outside of the body (*ex vivo*).[146] Examples include cells that have been propagated, expanded, selected, pharmacologically treated or otherwise altered in their characteristics.[147] Somatic cell products encompass autologous or allogeneic lymphocytes, cultured cell lines intended to secrete a bioactive factor or factors such as insulin or growth hormone, and autologous or allogeneic cells such as hepatocytes and fibroblasts.

Gene therapy products are those containing genetic material administered to modify or manipulate the expression of genetic material in the recipient or to alter the properties of living cells.[148] Those containing viral vectors are biological products, but other gene products, such as those that are chemically synthesized, are not. They are regulated as drugs solely under the FDCA.[149] An example of this exception for chemically synthesized products is a synthetic DNA or RNA sequence intended to alter a specific genetic sequence in human somatic cells after

[141] Department of Health and Human Services, National Institutes of Health, Recombinant DNA Research: Proposed Actions Under the Guidelines, Notice, 61 Fed. Reg. 59,726 (1996).

[142] For a description of the NIH regulation of gene therapy experiments, see Joseph M. Rainsbury, BIOTECHNOLOGY ON THE RAC—FDA/NIH REGULATION OF HUMAN GENE THERAPY, 55 FOOD & DRUG L.J. 575 (2000), and Richard A. Merrill & Gail H. Javitt, *Gene Therapy, Law & FDA Role in Regulation*, *in* ENCYCLOPEDIA OF ETHICAL, LEGAL, AND POLICY ISSUES IN BIOTECHNOLOGY 321 (Thomas J. Murray & Maxwell J. Mehlman eds., 2000).

[143] *See, e.g.*, Merrill and Javitt, *supra*.

[144] Food and Drug Administration, Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248 (1993).

[145] *Id.* at 53,249.

[146] *Id.*

[147] *Id.*

[148] *Id.*

[149] *Id.*

administration.[150] Other biologics include *ex vivo* transduced cells,[151] which basically are cells containing transferred genetic information through the use of viral agents that infect bacteria.

These categorizations are reminiscent of the product assignments to CBER or CDER as part of the 1991 intercenter agreements. As with those assignments, the rationale for these listings of products as biologics is not explained. Nevertheless, the same types of analyses pertaining to intact cells and viral vectors are applicable and some judicial analysis is available.

One court that has considered the status of cells as biologics ruled that rabbit and human fetal cells used for the treatment of diabetes were immunological agents subject to licensure as biological products (and as unapproved new drugs). In *United States v. Loran Medical Systems*,[152] it reasoned that, under 21 C.F.R. § 600.3(h)(5)(iii), such cells were analogous to a toxin or antitoxin used in the treatment of disease through a specific immune process.[153]

Although the human immune system usually rejects such implanted cellular material, the product was used in a way that specifically evaded an immune response. The government argued that this evasion involved a "specific immune process."[154] Defendants cited the Fifth Circuit's decision in *Blank* that blood and plasma were not analogous to a therapeutic serum because they were not employed for immunological purposes.[155] They also noted that, just as the *Blank* court's observation about blood transfusions were unknown to Congress when it enacted the PHSA in 1902, the human and rabbit cells in question were also unknown when the law was last amended.[156]

In rejecting *Blank*, the court noted that FDA had not promulgated regulations that could be read to include blood within the definition of a product analogous to a therapeutic serum.[157] It further stated[158] that the *Blank* decision was contrary to the Supreme Court's decision in *Permian Basin Area Rape Cases*, where it held that administrative agencies can adapt to changing circumstances.[159]

The court's reasoning in rejecting *Blank* because of the absence of applicable regulations covering blood seems flawed. Moreover, the rationale for applying the analogous products language involving a toxin or antitoxin is disingenuous. FDA had promulgated regulations that covered blood at the time of the *Blank* decision, but the court rejected their applicability because they were not adopted earlier at the time of the reenactment of the PHSA in 1944.[160] The same definitional regulations existed at the time of the decisions in both *Blank* (1968) and *Loran* (1986), as the last relevant substantive revisions to them occurred in 1961 (Table II). More fundamentally, the *Loran* court's rationale that a cell product that functions by *not* triggering a presumed specific immune response is nonetheless still covered by section 600.3(h)(5)(iii) is contrary to the actual definitional language of this regulation.

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[150] 58 Fed. Reg. at 53,251.
[151] *Id.*
[152] 25 F. Supp. 2d 1082 (C.D. Cal. 1997).
[153] *Id.* at 1085.
[154] *Id.* at 1084.
[155] *Id.* at 1085.
[156] *Id.*
[157] *Id.*
[158] *Id.*
[159] 390 U.S. 747, 784 (1968).
[160] 400 F.2d at 304 n.10.

If a substance does not treat a disease through a specific immune process, it cannot be analogous to a toxin or antitoxin.

Whatever shortcomings exist with the *Loran* decision, it did aptly address the issue of whether the cells in question were biological products covered by FDA's somatic cell therapy policy. Defendants argued that the cells were not covered by the policy since they were not biologically or genetically altered in any way.[161] The court pointed out that "[N]othing in the regulation [600.3(h)(5)(iii)] *requires* alteration before product is to fall under the FDA's purview."[162] Both were correct at least in certain respects. The defendants, about the scope of the somatic cell therapy policy and, the court, about the applicable regulation does not require product alteration. This latter observation actually is relevant to all the biological regulatory definitions yet today. The defendant's comment about the lack of coverage of the agency's somatic cell therapy policy of unaltered cells was eventually remedied in a further FDA notice, discussed next.

1. *HCT/Ps*

Building more upon the 1991 intercenter agreements, as well as on the above somatic cell and gene therapy notice, FDA began to focus on the precise triggers for requiring premarket clearances of newer cellular and other products as biologics. In March 1997, it proposed a comprehensive, detailed plan for the regulation of cells and collections of cells in the form of tissues. This plan covers human cells, tissues and cellular- and tissue-based products (HCT/Ps).[163] What it does not address, as usual, is why HCT/Ps are regulated as biologics in the first place. Their biological status seems presumed, perhaps based on the previous positions articulated by FDA in its intercenter agreements and somatic cell and gene therapy notice. The analyses there thus apply equally here.

The importance of the HCT/Ps initiative is again that it expands the universe of products that are biologics. In promulgating the new plan, the agency states that HCT/P regulation has been highly fragmented and it has not clearly defined criteria for when and how such products could be regulated.[164] Also noted was that new biotechnology methods "enhance and expand the use of human cells and tissues as therapeutic products," and that they hold promise for providing therapies for cancer, AIDS, Parkinson's disease and other serious conditions.[165]

The basic approach of the proposal is to divide HCT/Ps into two basic categories: products that are regulated as biological drugs (or devices) requiring premarket clearances and those that are regulated solely under section 361 of the PHSA, as reflected in new part 1271.[166] Section 361 provides authority to FDA to issue regulations to prevent the spread of communicable diseases.[167] The agency had previously used this authority to require testing and screening of tissue donors for

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[161] 25 F. Supp. 2d at 1085.

[162] *Id.* at 1085-86 (footnote omitted) (emphasis in the original).

[163] *See* Food and Drug Administration, Proposed Approach to Regulation of Cellular and Tissue Based Products, 62 Fed. Reg. 9721 (1997) (announcing availability of a document entitled "Proposed Approach to Regulation of Cellular and Tissue Based Products," which was never published in the *Federal Register*). The Proposed Approach is available at www.fda.gov/cber/gdlns/celltissue.pdf.

[164] Proposed Approach, *supra*, at 3.

[165] *Id.*

[166] 21 C.F.R. pt. 1271.

[167] *See* 42 U.S.C. § 264.

hepatitis and human immunodeficiency viruses.[168] HCT/Ps that are subject only to regulation under section 361 must meet part 1271 requirements involving product registration and listing, donor eligibility, good tissue practices, and reporting and inspection, but not premarket clearances.[169] Those that are biological drugs or devices are subject to premarket clearance requirements and to related registration and listing requirements of the FDCA, as well as to the donor eligibility procedures and good tissue practice provisions of part 1271.

New part 1271 applies to HCT/Ps that are minimally manipulated, are not promoted or labeled for any use other than homologous use,[170] have not been combined with and modified by addition of noncellular or nontissue components, and do not have a systemic effect.[171] Said somewhat differently, if any one of these criteria is not met, then the product is at least subject to licensure as a biological drug.

Two key categories insofar as biological drugs and modern biotechnology methods are concerned are products that are more than minimally manipulated and those that have system effects. As FDA noted in its somatic cell and gene therapy notice, cells subject to licensure as biological products include those that have been manipulated in a way that changes the characteristics of the cell population.[172] Examples of "more than minimal manipulation" in the new plan again include cell expansion, encapsulation, activation, or genetic modification, but not cell selection.[173]

The other category pertaining to HCT/Ps that have systemic effects involves those having a metabolic function. HCT/Ps that are dependent upon metabolic activity for their primary function require licensure as biologics unless they are for autologous use, for transplantation into a first degree or second degree blood relative, or are for reproductive use.[174] A relevant example is reproductive cells, which are not covered by FDA's 1993 policy relating to somatic cells because they are germ line cells. Although they have a metabolic function, typically in an allogeneic setting, they would not be subject to premarket clearances as biologics unless they meet one of the other criteria, such as where they are more than minimally manipulated.[175]

Other examples exist of biological products that require licensure because they are more than minimally manipulated or have systemic effects. These include hemapoietic, stem, and other cells that have been expanded or modified as part of gene therapy, cloned and/or are activated lymphocyte therapies for cancer and infectious diseases, and pancreatic islet cells, except when used for autologous or allogeneic use in a first degree or second degree blood relative.[176] The last biological

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[168] *See* 21 C.F.R. pt. 1270.

[169] *Id*. pt. 1271, subparts B (Procedures for Registration and Listing), C (Donor Eligibility), D (Good Tissue Practices), E (Additional Requirements for Establishments), and F (Inspection and Enforcement of Establishments).

[170] Homologous use involves the replacement or supplementation of recipient cells or tissues within HCT/Ps that perform the same basic function or functions in the recipient as in the donor. 21 C.F.R. § 1271.3(c). An example would be hemapoietic stem cells used for hemapoietic reconstitution. Proposed Approach, *supra* note 163, at 15. *See also* RFD 2002.016, Amniotic Membrane for Ocular Surface Reconstruction (upon reconsideration by FDA, ocular application of amniotic membrane tissue deemed to be homologous use), *available at* http://www.fda.gov/oc/combination/rfd.html.

[171] *Id*. pt. 1271.10.

[172] 58 Fed. Reg. at 53,248.

[173] Proposed Approach, *supra* note 163, at 14.

[174] *See* 21 C.F.R. § 1271.10(a)(4)(ii).

[175] *See Proposed Approach*, *supra* note 163, at 16-17, 20. *See also* 21 C.F.R. pt. 1271.10(a) and *infra* note 203 and accompanying text.

[176] 63 Fed. Reg. at 6746 and Proposed Approach, supra note 163, at 16, Table 1, C.3.

product area covering metabolic or systemic cells, such as pancreatic cells, is a new category that could have covered the cells that had no manipulation in the *Loran* case discussed previously.[177]

Important products that are not considered HCT/Ps are vascularized human organs for transplantation, whole blood or blood components, such as red blood cells, platelets, and plasma, xenograft transplants, and products that are secreted by or extracted from cells or tissues, such as human milk, cytokines, and other growth factors.[178]

D. *Veterinary Biological and Nonbiological Drugs*

The applications of recombinant DNA methods or so-called bioengineering to nonhuman animals also are myriad. The two major uses are similar to those in the human area. As in the bovine interferon example, of primary interest are those products that are *not* biological drugs, particularly in light of the status as biologics of their human counterparts.

The two key uses involve employing genetically engineered cells as production factories for veterinary drugs[179] and the bioengineering of animals themselves. An initial production use involved recombinant bovine somatotropin (rBST), or growth hormone, to increase milk production, a controversial product[180] that was approved by CVM as a new animal drug under the FDCA.[181] The nonbiological drug status of rBST is not surprising, since the immune system is not primarily involved, a characteristic of most hormones.

Of more particular complexity, as in the human biologics gene therapy area, are the other applications of bioengineering to nonhuman animals themselves. These uses include the production of pharmaceuticals for human or veterinary use. The former human application has been discussed previously, in the context of the example of the production of human antibodies in goats. A common illustration of the other veterinary use is fish that have been genetically engineered to produce

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[177] *See supra* note 152 and accompanying text.

[178] 21 C.F.R. § 1271.3(d)(2). *See also* Food and Drug Administration, Establishment Registration and Listing for Manufacture of Human Cellular and Tissue Based Products, Proposed Rule, 63 Fed. Reg. 26,744, 26,745 (1998).

[179] Similar to FDA, APHIS has promulgated a number of documents pertaining to new biotechnology products and has licensed as biologics a number of such products involving the immune system, including a variety of monoclonal antibody products such as for canine lymphoma. *See, e.g.*, Center for Veterinary Medicine, Veterinary Services Memorandum No. 800.205, General Licensing Considerations: Biotechnology-Derived Veterinary Biologics, Categories I, II, and III (May 28, 2003); Center for Veterinary Biologics, Veterinary Services Memorandum No. 800.68, New Biotechnology for Preparation of Animal Biological Products (Dec. 4, 1984), and Center for Veterinary Biologics, Risk Analysis for Veterinary Products, *at* www.aphis.usda.gov/vs/cvb/html/vsmemos.html. *See also* Veterinary Biological Products, *supra* note 124, and Edward L. Korwek, 1997 UNITED STATES BIOTECHNOLOGY REGULATIONS HANDBOOK, App. IV, p. 701 (containing an early list of licensed new biotechnology biological products as of Apr. 25, 1997).

[180] *See, e.g.,* U.S. Congress, Office of Technology, *U.S. Dairy at a Crossroad: Biotechnology and Policy Choices* (1991). *See also* B. Corey, *Bovine Growth Hormone: Harmless for Humans*, FDA CONSUMER Apr. 1990; Food and Drug Administration, Notice, Guidance on Labeling of Milk from Non-BST Treated Cows, 59 Fed. Reg. 6279 (1994); International Diary Foods Ass'n v. Amestoy, 92 F.3d 67 (2d Cir. 1996) (successful constitutional challenge to state statute requiring labels for products from cows treated with bovine growth hormone); and *Advocacy Groups Hope Codex Ruling Leads to rBGH Suspension*, FDA WEEK, at 9 Mar. 2, 2007.

[181] *See* U.S. Food and Drug Administration, Center for Veterinary Medicine, Report on the Food and Drug Administration's Review of the Safety of Recombinant Bovine Somatotropin, *available at* http://www.fda.gov/cvm/RBRPTFNL.htm.

growth hormone to make them larger.[182] Another example includes nonhuman animals that are engineered to be disease-resistant or that have desirable food production characteristics, such as leaner meat.[183]

These varied *in vivo* uses of bioengineering or recombinant DNA methods to create so-called transgenic nonhuman animals often have been stated as triggering the new animal drug application (NADA) provisions of the FDCA, including the investigational requirements pertaining to experimental use.[184] Unlike the situation in the human area, however, the genetic construct and its expression product, such as the growth hormone in the fish example, would be considered a new animal drug.[185] Although not without controversy, primarily because of the limitations of the NADA process to assess environmental concerns,[186] such regulation has not engendered any debate about whether APHIS biologics jurisdiction should apply instead. The biological status of similar genetic constructs involved in human gene or cell therapy seems relevant. Even though a significant difference between the human and these other animal applications is that the latter typically are intended to encompass heritable changes, whereas the human uses are not, the techniques involved are still fundamentally the same.

An early governmental assessment of the possible applications of bioengineering to nonhuman animals seems to acknowledge the possibility of APHIS regulation, but dismisses it rather summarily. In a case study involving growth-enhanced salmon, it notes that "transgenic Atlantic salmon are subject to … oversight [by CVM] because they are considered to contain a 'new animal drug.'"[187] This statement contains a footnote nonetheless acknowledging that "fish modified to contain or produce a veterinary biologic can be subject to regulation by APHIS under [VSTA] … rather than by FDA under the [FDCA]."[188] No other clarifying commentary seems to exist on the biologics option.[189]

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[182] *See, e.g.*, A Martin, *One fish, two fish, genetically new fish*, CHICAGO TRIBUNE Nov. 12, 2003 at A1. *See also infra* note 185.

[183] *See, e.g.*, *Issues in Regulation of Genetically Engineered Plants and Animals*, at 101, PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY (Apr. 2004).

[184] CVM reported in 2003 that it had investigated the improper disposal of bioengineered pigs that may have entered the food supply but that apparently posed no public health risks. *See* Food and Drug Administration, Food and Drug Administration Talk Paper, FDA Investigates Improper Disposal of Bioengineered Pigs (Feb. 5, 2003), *available at* http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01197.html. *See also* Letter from Gloria J. Dunnavan, Director, Division of Compliance, Office of Surveillance and Compliance, CVM, to Melanie J. Loots, Associate Vice Chancellor for Research, Univ. of IL at Urbana-Champaign (Sept. 29, 2003) (advising of violations of CVM investigational new animal drug regulations), *available at* http://www.fda.gov/cvm/FOI/UIUCLetter.htm, and the Department of Health and Human Services, Food and Drug Administration, Form 483, Inspectional Observations (listing failure to monitor INADs regarding investigational transgenic pigs) (Jan. 1, 2003), *available at* http://www.fda.gov/ora/frequent/483s/3003291927_uill/FEI3003291927_02.html. *See also Issues in Regulation*, *supra* note 183, at 106-113, and *Future Fish, Issues in Science and Regulation of Transgenic Fish*, PEW INITIATIVE ON BIOTECHNOLOGY (Jan. 2003).

[185] *Future Fish, supra*, at 41 and *Issues in Regulation*, *supra* note 183, at 112.

[186] *See, e.g.*, *Issues in Regulation*, *supra* note 183, at 102-104, and *Future Fish, supra* note 184, at 42. *See also* Biotech in the Barnyard: Implications of Genetically Engineered Animals, Proceedings from a Workshop sponsored by the PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY (2002).

[187] *See* CEQ/OSTP Assessment: Case Studies of Environmental Regulation of Biotechnology, Case Study No. 1, Growth Enhanced Salmon, at 13 (2001)(footnote omitted), *available at* http://www.ostp.gov/html/012201.html. *See also* Council on Environmental Quality, Office of Science and Technology Policy, Notice of Availability and Request for Comments, 66 Fed. Reg. 7905 (2001) (announcing availability of case studies and inviting comment).

[188] *Case Studies*, *supra*, at 13 n.2.

[189] *See also* Food and Drug Administration, Center for Veterinary Medicine, Information for Consumers, Questions and Answers About Transgenic Fish, *at* http://www.fda.gov/cvm/transgen.htm (stating, "Most, but

This difference in the regulatory treatment as biologics of human and veterinary products probably is based on the view that the genetic constructs and their products involved in most veterinary applications do not involve the immune system or an immune response. Such an interpretation is consistent with APHIS's regulations, as discussed below. Nevertheless, it is also fairly easy to envision exceptions that would seem to fall squarely within APHIS's jurisdiction, such as a genetic insert producing viral antigens that possibly trigger CMI or AMI. Admittedly, even in this example, though, the genetic construct does not itself function through an immune process, which would probably hold true for most applications of recombinant DNA methods.

E. *Human and Other Animal Cloning*

No modern biotechnology topic area has prompted as much public, legislative, legal, ethical and regulatory controversy as cloning. The term can be very loosely defined as the creation of "a precise genetic copy of a molecule, cell, plant, animal, or human being."[190] Because cloning can include an assortment of different old and newer techniques, any meaningful regulatory discussion of the topic must focus on a specific technology. Certain types of reproductive cloning have been around for quite some time in the plant and livestock industries to create improved food sources.[191] Cloning can also be used to generate cells, tissues, or organs, including from nonhuman animals, for the purposes of the treatment of human diseases, sometimes called "therapeutic cloning."

The creation of Dolly the Sheep, which has generated much of the controversy, utilizes a more complex type of reproductive cloning called "somatic cell nuclear transfer" (SCNT). The nucleus from an egg cell is removed (enucleated) and replaced with one from a donor somatic cell—in Dolly's case, a cell from another sheep's mammary glands. Cellular division of the egg cell is triggered resulting in an embryo, which is implanted, in this example, in another sheep that gave birth to Dolly, a genetic clone of the donated cell or donor organism.[192]

The potential applicability of SCNT to human cloning initially created a firestorm of federal activity. President Clinton imposed an administrative ban on federal funding of attempts to clone human beings.[193] A number of bills were proposed, including one proposed by the Clinton administration entitled The Cloning Prohibition Act of 1997.[194] The debate, which eventually subsided for awhile, accelerated to an almost circus-like atmosphere when Dr. Richard Seed announced a plan to clone a human being.[195] On the veterinary side, a similar but not quite as vociferous

probably not all, gene-based modifications of animals for production or therapeutic claims fall under CVM regulation as new animal drugs.").

[190] *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission (NBAC)*, NATIONAL ETHICS ADVISORY COMMISSION 13 (1997).

[191] *See id.* at 14 and 26.

[192] *Id.* at 22.

[193] *See Memorandum on the Prohibition of Federal Funding for Cloning of Human Beings*, 33 WKLY. COMP. PRES. DOC. 281 (1997).

[194] *See Clinton Urges Ban on Cloning of Humans*, 114 CHRISTIAN SENTRY 583 (1997). *See also* Diane M. Ginelli, *Congress Weighs Ban on Cloning: Bills Differ on Research Issues*, AM. MED. NEWS, Feb. 23, 1998, at 3; Lisa Seachrist, *Feinstein, Kennedy, Offer Bill to Ban Human Cloning*, BIOWORLD TODAY, Feb. 3, 1998, at 1. For an extensive discussion of cloning legislation, see G. Rokosz, *Human Cloning, Is the Reach of FDA Authority Too Far a Stretch?*, 30 SETON HALL L.R. 464 (1999-2000).

[195] *See, e.g.*, *Human Cloning Within Two Years? Chicago Scientist Talks of "Becoming One With God,"* S.F. EXAMINER, Jan. 7, 1998, at A1. Numerous accounts have been published on the legal and other aspects

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controversy has recently embroiled SCNT methodology utilized in animal cloning for food production,[196] which CVM has said is safe.[197] Although a petition has been submitted to regulate such animal cloning, also under the new animal drug provisions of the FDCA,[198] CVM has not yet responded.

Insofar as FDA's jurisdiction over human cloning by SCNT is concerned, a few positions have been articulated.[199] SCNT has simply been characterized as another form of gene therapy, which the agency already regulates.[200] It also has been described as subject to the biological provisions of the PHSA, as well as to the drug and device provisions of the FDCA. This includes the statutory authorities applicable to human somatic cell and gene therapies and to HCT/Ps.[201] Again, none of these positions articulate what aspects of SCNT precisely trigger biological status, a topic that has been exceptionally contentious for a variety of legal and other reasons not always related to regulatory jurisdictional issues.[202]

Nevertheless, as FDA suggests, a number of similarities do exist among somatic cell and gene therapy products, HCT/Ps, and SCNT. The enucleated reproductive cell that is created is obviously more than minimally altered under FDA's HCT/Ps plan and regulations, especially after having been further manipulated to contain the nucleus of a somatic cell, which also has been more than minimally manipulated after removal of its nucleus. The transferred nucleus [203] containing genetic information is similar to a viral vector used in gene therapy. Thus, the enucleated recipient reproductive cell, the donor enucleated somatic cell, and the resultant genetically modified reproductive cell are all subject to regulation as biologics, as is the nucleus containing genetic information that is transferred.

Whatever the merits of the foregoing subject matter discussion, it is incomplete. Use considerations can potentially present an even more difficult analysis. Although therapeutic cloning used to develop cells and tissues for the treatment of human diseases or other conditions could seemingly easily fall within the language involv-

of human cloning. *See, e.g.*, June Kolata, *On Cloning Humans, "Never" Turns Swiftly into "Why Not,"* N.Y. TIMES, Sept. 2, 1997, at A1, *Feds: Cloning Is Regulated, FDA Says Procedure Requires Approval*, NEWSDAY (N.Y.), Jan. 21, 1998, at A20. Elizabeth C. Price, *Does the FDA Have Authority to Regulate Cloning*, 11 Harvard Journal of Law and Tech. 619 (1998); Richard A. Merrill & Brian J. Rose, *FDA Regulation of Human Cloning?, Use of Patience or Statesmanship?,* 15 Harv. J.L. & Tech. 86 (2001-2002); and Rick Weiss, *Human Cloning Will Be Regulated: FDA Asserts It Has Statutory Authority to Regulate Attempts at Human Cloning*, WASH. POST, Jan. 20, 1998, at A1.

[196] *See, e.g.,* Animal Cloning and the Production of Food Products: Perspectives from the Food Chain, Proceedings from a Workshop sponsored by the Pew Initiative on Food and Biotechnology and the Center for Veterinary Medicine of the U.S. Food and Drug Administration (2002).

[197] *See generally* Food and Drug Administration, Draft Animal Cloning Risk Assessments; Proposed Risk Management Plan; Draft Guidance for Industry; Availability, Notice, 72 Fed. Reg. 136 (2007).

[198] Center for Food Safety et al., Citizen Petition, Petition Seeking Regulation of Cloned Animals, 2006P-0415, Oct. 12, 2006, *available at* www.fda.gov/OHRMS/DOCKETS/DOCKETS/06p0415/06p0415.htm.

[199] *See generally* Food and Drug Administration, Center for Biologics Evaluation and Research, Use of Cloning Technology to Clone Human Being, *at* www.fda.gov/cber/genetherapy/clone.htm.

[200] *See Human Cloning, supra* note 195, at A1 (citing comments of Dr. Michael Friedman, FDA's Acting Commissioner during a public radio call-in show).

[201] *See Issues Raised by Human Cloning Research: Hearing Before the Subcomm. on Oversight and Investigations of the House Comm. on Energy and Commerce*, 107th Cong. 78-81 (2001) (statement of Dr. Kathryn Zoon, Director, CBER, FDA). The Internet address in note 199 contains a link to Dr. Zoon's testimony.

[202] *See supra* note 195 and accompanying text. *See also Cloning Symposium*, 38 JURIMETRICS 1-97 (Fall 1997) (containing 12 articles on various aspects of cloning).

[203] The nucleus of a somatic cell (which is diploid, containing 46 chromosomes) used in a reproductive cell (which is haploid, containing 23 chromosomes) might be considered nonhomologous use under the HCT/P Proposed Approach and Part 1271 regulations, although nuclei are not cells, but organelles.

ing "prevention, treatment or cure of a disease or condition," reproductive cloning is more troublesome. It would apparently trigger only the "condition" component of this quoted language, if at all. Use of reproductive cloning for infertility purposes would presumably be covered, but such cloning does not necessarily always have to involve a "condition." It can be used for purposes unrelated to any bodily condition, much like other reproductive techniques.

F. *Modernization of the Veterinary Biologics Definition: Subject Matter Emphasis*

In 1997 APHIS updated its biologics regulatory definitions for a variety of reasons. It did so in response to a citizens' petition from a trade association[204] and as a result of advances in understanding how veterinary biologics work.[205] The agency noted that its biologics regulations had not been amended since 1973; multiple components can interact in the functioning of the immune system; certain immunomodulators are biologics, as are genetically engineered products; and blood or blood components are involved in passive or active immunization.[206]

The importance of these modified provisions cannot be overemphasized in terms of their subject matter orientation.[207] Although not perfect, as few regulations are, they constitute a giant step forward in setting forth common, relatively simple criteria that define a biologic. They not only try to address many of the limitations and ambiguities of the veterinary biological statute and previous regulations, but they do so through the use of informal rulemaking procedures.

The regulations clarify that products are biologics if they typically involve the immune system, not necessarily a specific immune mechanism. Only diseases are covered, not other conditions such as infertility. Antibiotics are specifically excluded, and diagnostics for diseases (not conditions) are included if they involve measurement of immunity or of certain immune components and nucleic acids.[208] More important, a key indicator of veterinary biologic status is how the product functions, a theme that is consistent with the legislative history of VSTA. Just as significant, this rather singular criterion represents an approach that obviously is very different from that involving the very diverse, multiple criteria that apply to human biological status.

The focus is on products "which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response."[209] In other words, a biological product apparently cannot, for example, act secondarily through direct stimulation, or primarily through indirect stimula-

[204] Animal Health Institute, Citizen Petition, Doc. No. 93P-0337 (Sept. 11, 1995).

[205] *See* 62 Fed. Reg. at 31,327.

[206] Animal and Plant Health Inspection Service, Viruses, Serums, Toxins, and Analogous Products; Definition of Biological Products and Guidelines, Proposed Rule, 61 Fed. Reg. 43,483, 43,484-43,485 (1996).

[207] The use provision changes were previously discussed in Part III.A.3. *See supra* notes 48-50 and accompanying text.

[208] Diagnostics are defined as substances for the treatment of animals "through the detection or measurement of antigens, antibodies, nucleic acids, or immunity." 9 C.F.R. § 101.2(2)(ii).

[209] APHIS explains that for purposes of the rule

> 'Stimulation' would refer to 'active immunization' and 'supplementation' of the immune system when referred to 'passive immunization' (by blood or other components). 'Enhancement' or 'modulation' of the immune system would refer to the 'up regulation' or 'fine tuning,' respectively, of the immune system in the generation of an effective immune response.

61 Fed. Reg. at 43,484.

tion. Admittedly these are potentially formidable standards to meet in every case. Detailed information about a product's specific mechanism of action can sometimes be difficult to ascertain or prove. Nonetheless, at least the immune basis of the regulations is clarified and broadened, compared to the early approach involving "a specific immune reaction."

The types of biological products that are specifically named are vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components that are of natural or synthetic origin or that are derived from synthesizing or altering various substances or components of substances, such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.[210]

In referencing "certain" cytokines, the agency appropriately notes that such substances can be produced in many tissues and can act on different cell types, but that some can also serve as essential components in the generation and expression of an immune response, such as interleukins.[211] Thus, not all products that are cytokines would necessarily be regulated under VSTA, a position that is consistent with the bovine interferon decision in 1982.

The analogous products definitions are much broader. They mention, in part, substances that "are similar in function to biological products in that they act or are intended to act through the stimulation, supplementation, enhancement or modulation of the immune system or immune response."[212] Whether the absence of repeat language requiring such products to act "primarily through direct" stimulation, and so forth, of the immune system is purposeful is unclear. The omission may not matter, however, since the "intended to act" terminology seems to suggest how such analogous products actually function *in vivo* is immaterial. This absence of an actual mechanism of action requirement as part of the analogous products definitions is repeated elsewhere. A product is also analogous if it "resembles" or is "represented" as a biological product through appearance, packaging, labeling, "or any other means."[213]

Both of these definitions for analogous products seem to cover a vast range of products. How the products actually function, their source or other characteristics do not seem to matter. Indeed, APHIS states in preamble language to the proposed and final rules that "water and coloring," which "appears" to be a biological product, or that is packaged or labeled or otherwise represented as a biological product, will be considered an analogous product.[214] This approach to categorizing a product as a biologic is confusing, as it suggests that what a product is called determines biologic status, regardless of its actual or objective characteristics.[215] In the context of bovine interferon mentioned previously, describing it as a biologic would have made it so, it seems, thus possibly precluding CVM jurisdiction.

The agency also makes clear that its regulatory definitions of biological products cover "natural" or synthetic products and allergens,[216] unlike FDA's regulations.

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[210] *See* 9 C.F.R. § 101.2.

[211] 62 Fed. Reg. at 31,327.

[212] 9 C.F.R. § 101.2(2)(i).

[213] *Id.* § 101.2(2)(iii).

[214] 61 Fed. Reg. at 43,485 and 62 Fed. Reg. at 31,327.

[215] On the other hand, the regulations state that intended use is determined by an objective standard. *See* 9 C.F.R. § 101.2(1).

[216] *Id.* § 101.2. Licensed veterinary allergenic extracts include house dust, mixed trees, mixed insects, mixed food, and flea antigen. *See* Veterinary Biological Products, *supra* note 124.

The language in the opening part of the definition quoted previously referring to a variety of named "biological products," such as vaccines, also references those that "are of natural or synthetic origin."[217] APHIS further notes that live or killed vector systems that carry immune components already fall under the biologics definition.[218] The regulations also state that antibiotics are not toxins.[219] Hormones are not specifically excluded, presumably because they usually do not "act primarily through direct" stimulation, supplementation, enhancement, or modulation of the immune system or immune response. Whole blood and plasma also are not covered, since whole blood used for the replacement of blood volume would not be a biological product, according to APHIS.[220] This position seems consistent with the decision in *Blank*.

V. CONCLUSION

Two very similar original recipes existed for biologics. The one for human beings has evolved more elaborately, at least initially, into a series of other derivative recipes utilizing a complex mixture of ingredients that have certain characteristics, function in a specific way, or are obtained from "natural" sources.

These follow-up human recipes are quite dated, having had their last major rework in 1947. They are time worn and tattered; sometimes read or misread to result in products that on occasion are seemingly very different from those produced by the original recipe. The derivative recipes are especially difficult and tedious to follow for newer biologics, because they do not always spell out all of the necessary details, leaving room for interpretative differences and controversy. To potentially make matters even more difficult, many interpretations of them since the early 1980s have not been reflected in the actual recipes themselves.

The other original veterinary recipe has evolved very little since 1913, until derivative recipes were developed relatively recently in 1991. Nevertheless, the recipes over the years have fairly consistently been interpreted to involve only ingredients that function in a certain general way, a very different approach from that of the human recipes. As a result, the newer derivative veterinary recipes adopted in 1991 are often easier to follow, although they are not perfect, as few recipes are. They also are more accommodating of modern technological developments. Indeed, products of the derivative recipes seem to have many characteristics in common with the products of the original recipe adopted in 1913.

The two sets of recipes are similar or different in several key respects. Both cover allergens and immune-based products; neither covers hormones or antibiotics. Blood and arsphenamine products are included in the human recipes but not in the veterinary versions, largely because the basic original recipe for human biologics was officially changed in 1944. This difference is therefore understandable, as is the contrast between the use provisions of the recipes, also officially changed in 1944 and 1997 on the human side. The human recipes include all diseases and other conditions; the veterinary ones, only conditions that are diseases.

Another important difference is that the human recipes often have been interpreted, it seems, to place undue emphasis on the "natural" source of the ingredients, to the point where ingredients that are obtained differently often are not included.

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[217] 9 C.F.R. § 101.2. *See also* 62 Fed. Reg. at 31,328.
[218] 62 Fed. Reg. at 31,328.
[219] *See* 9 C.F.R. § 101.2.
[220] 61 Fed. Reg. at 43,485.

The veterinary recipes are not so limiting. Also, cell culture products, gene therapies and cloning often are considered to be included in the human biological recipes, but the same is not generally true for their veterinary counterparts, unless they function in a certain general way.

In short, there appear to be more differences than similarities in the two sets of recipes as they have evolved over the past one hundred years. Some of the contrasts can easily be explained; others, not so easily, or not without a good measure of patience and perseverance in parsing the words. On the other hand, the human recipes often had to be tried and tested first, resulting in their almost forcible evolution contemporaneously with the development of newer products. Once a recipe works, why change? It's hard to argue with success.

Notwithstanding these considerations, both sets of recipes for human and other animal biologics are complex. Trying to follow and understand them, even today, is a challenge. Reading the recipes accurately and making the "brew" is not for the untrained or inexperienced. Many commentators, courts, and others have tried but few, if any, have succeeded, particularly in deciphering the human versions. From these perspectives, another possible recipe is much simpler and easier to follow, that for a drug under the FDCA. It is good as a first try or even better as a standby, particularly when the biological recipes do not work or are too complicated to follow. This point can possibly help explain why both sets of recipes for biologics evolved as they have, sometimes very differently.

Table I
Excerpted Human Biologics Statutory Definitional Changes

Date/Source	HUMAN STATUTORY LANGUAGE
1902 Pub .L. No. 57-244, ch. 1378, 32 Stat. 728 (July 1, 1902)	Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man
1944 Pub. L. No. 78-410, ch. 373, 58 Stat. 682, 702 (July 1, 1944)	Any virus, therapeutic serum, toxin, antitoxin, or analogous product**, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound),** applicable to the prevention ~~and~~**, treatment, or** cure of diseases **or injuries** of man
1970 Pub. L. No. 91-515, § 291, 84 Stat. 1297, 1308 (Oct. 30, 1970)	Any virus, therapeutic serum, toxin, antitoxin, **vaccine, blood, blood component or derivative, allergenic product,** or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man
1997 Pub. L. No. 105-115, § 123(d), 111 Stat. 2295, 2324 (Nov. 21, 1997)	~~Any~~ **'Biological product' means a** virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or ~~its derivatives~~ **derivative of arsphenamine** (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of ~~diseases~~ **a disease** or ~~injuries~~ **condition** of ~~man~~ **human beings.**

Table II
Excerpted Human Biologics Regulatory Definitional Changes

Date/Source	Human Regulatory Language
1909 Treasury Department, U.S. Public Health and Marine-Hospital Service, Regulations for the Sale of Viruses, Serums, Toxins, and Analogous Products in the District of Columbia and in Interstate Commerce, ¶ 16	[Previous regulations initially adopted in 1903 did not define biologics] Antidiptheric serum or diphtheria antitoxin, antitetanic serum or tetanus antitoxin, antistreptococcic serum, antistaphylococcic serum, antigonoccic serum, antipneumococcic serum or antipneumonic serum, antidysenteric serum, antituberculous serum, antipest serum, anticholera serum, streptolytic and pneumolytic serum, antimeningococcic serum, antiplague serum, erysipelas and prodigiosus toxins, tuberculins, emulsion tubercle bacilli, suspension of lactic acid bacilli, antityphoid serum, bacterial vaccines, normal horse serum, and vaccine virus.
1919 Treasury Department, U.S. Public Health and Marine-Hospital Service, Regulations for the Sale of Viruses, Serums, Toxins, and Analogous Products in the District of Columbia and in Interstate Commerce, Miscellaneous Publication No. 10, ¶ 7	[Previous 1909 language completely deleted] **Viruses, serums, toxins, antitoxins, and analogous products applicable to the prevention or cure of diseases of man are referred to as biologic products and defined as follows: I. A virus is a product containing the minute living cause of an infectious disease. II. A serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells. III. A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of one milliliter or less of the product, and having the property, following the injection of nonfatal doses into an animal, of producing therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. IV. An antitoxin is a product containing the soluble substance in the serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. V. An analogous product is (a) prepared from a virus, including microorganisms actually or potentially virulent, or (b) prepared from some constituent of the blood, or (c) intended for specific immunization or therapy.**

DATE/SOURCE	HUMAN REGULATORY LANGUAGE
1923 Treasury Department, U.S. Public Health and Marine-Hospital Service, Regulations for the Sale of Viruses, Serums, Toxins, and Analogous Products in the District of Columbia and in Interstate Commerce, Miscellaneous Publication No. 10, ¶ 7	Viruses, serums, toxins, antitoxins, and analogous products applicable to the prevention or cure of diseases of man are referred to as biologic products and defined as follows: I. A virus is a product containing the minute living cause of an infectious disease. II. A serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells. III. A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of one milliliter or less of the product, and having the property, following the injection of nonfatal doses into an animal, of ~~producing~~ **causing to be produced** therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. IV. An antitoxin is a product containing the soluble substance in the serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. V. ~~An~~ **A product is** analogous ~~product is~~ (a) **to a virus if** prepared from a virus, including microorganisms actually or potentially virulent~~, or~~**;** (b) **to a serum, if** prepared from some **protein** constituent of the blood~~, or (c) intended for~~ **and intended for parenteral administration; (c) to a toxin or antitoxin, if intended, by parenteral administration, for the prevention or treatment of disease through** specific immunization ~~or therapy~~.

DATE/SOURCE	HUMAN REGULATORY LANGUAGE
1947 42 CFR § 22.1 (12 Fed. Reg. 410, 411-12)	~~Viruses, serums, toxins, antitoxins, and~~ **(g) "Biologic product" means any virus, therapeutic serum, toxin, antitoxin, or** analogous ~~products~~ **product** applicable to the prevention**, treatment** or cure of diseases **or injuries** of man ~~are referred to as biologic products and defined as follows:~~ **:** (~~a~~**1**) A virus is a product containing the minute living cause of an infectious disease. (~~b~~**2**) A **therapeutic** serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells **and intended for administration by a route other than ingestion**. (~~c~~**3**) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less **(or equivalent in weight)** of the product, and having the property, following the injection of ~~nonfatal~~ **non-fatal** doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. (~~d~~**4**) An antitoxin is a product containing the soluble substance in ~~the~~ serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. (~~e~~**5**) A product is analogous **:** (~~1~~**i**) ~~to~~ **To** a virus if prepared from ~~a virus, including micro-organisms~~ **or with a virus or agent** actually or potentially ~~virulent; (2) to a serum, if prepared from some protein constituent of the blood and intended for parenteral~~ **infectious, without regard to the degree of virulence or toxicogenicity of the specific strain** used**.** **(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum and intended for** administration~~; (3) to~~ **by a route other than ingestion.** **(iii) To** a toxin or antitoxin, if intended, ~~by parenteral administration~~ **irrespective of its source of origin**, for the prevention ~~or~~**,** treatment ~~of disease~~**, or cure of diseases or injuries of man** through specific immunization. **(h) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.** **(i) "Products" includes biologic products and trivalent organic arsenicals. A product is deemed "applicable to the prevention, treatment or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person; and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biologic product.**

DATE/SOURCE	HUMAN REGULATORY LANGUAGE
1960 42 C.F.R. § 73.1 (25 Fed. Reg. 3397, 3397-98)	(~~g~~**h**) "~~Biologic~~ **Biological** product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man: (1) A virus is a product containing the minute living cause of an infectious disease. (2) A therapeutic serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells and intended for administration by a route other than ingestion. (3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. (4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. (5) A product is analogous: (i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used. (ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum and intended for administration by a route other than ingestion. (iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, for the prevention, treatment, or cure of diseases or injuries of man through specific immunization. (~~h~~**i**) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man. (~~i~~**j**) "Products" includes ~~biologic~~ **biological** products and trivalent organic arsenicals. A product is deemed "applicable to the prevention, treatment or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person~~:~~**,** and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a ~~biologic~~ **biological** product.

DATE/SOURCE	HUMAN REGULATORY LANGUAGE
1961 42 CFR § 73.1 (26 Fed. Reg. 10355, 10355-56)	(h) "**Products" includes biological products and trivalent organic arsenicals.** **(i) "**Biological product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man: (1) A virus is **interpreted to be** a product containing the minute living cause of an infectious disease **and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa**. (2) A therapeutic serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells**,** and **not** intended for ~~administration by a route other than~~ ingestion. (3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. (4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. (5) A product is analogous: (i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used. (ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum**,** and **not** intended for ~~administration by a route other than~~ ingestion. (iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, ~~for~~ **to be applicable to** the prevention, treatment, or cure of ~~diseases~~ **disease** or injuries of man through **a** specific ~~immunization~~ **immune process**. (i**i**) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man. ~~(j) "Products" includes biological products and trivalent organic arsenicals.~~ **k)** A product is deemed "applicable to the prevention, treatment or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

DATE/SOURCE	HUMAN REGULATORY LANGUAGE
1968 42 CFR § 73.1 (33 Fed. Reg. 367, 367)	(h) "Products" includes biological products and trivalent organic arsenicals. (i) "Biological product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man: (1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa. (2) A therapeutic serum is ~~the~~ **a** product obtained from ~~the~~ blood ~~of an animal~~ by removing the clot or clot components and the blood cells~~, and not intended for ingestion~~. (3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. (4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. (5) A product is analogous: (i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used. (ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum~~, and not intended for ingestion~~. (iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process. (j) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man. (k) A product is deemed "applicable to the prevention, treatment**,** or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when intended~~,~~ through administration or application to a person~~,~~ as an aid in diagnosis**,** or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

DATE/SOURCE	HUMAN REGULATORY LANGUAGE
2006 (Current regulations) 21 C.F.R. § 600.3	(h) ~~*Products* includes biological products and trivalent organic arsenicals.~~ ~~(i)~~ *Biological product* means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man: (1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa. (2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells. (3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized. (4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune. (5) A product is analogous: (i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used. (ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum. (iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process. (**i**) *Trivalent organic arsenicals* means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man. (**j**) A product is deemed *applicable to the prevention, treatment, or cure of diseases or injuries of man* irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

Table III

Excerpted Veterinary Biologics Regulatory Definitional Changes

DATE/SOURCE	VETERINARY REGULATORY LANGUAGE
1913 U.S. Department of Agriculture, Bureau of Animal Industry – BAI Order No. 196, Regulations Governing the Participation, Sale, Barter, Exchange, Shipment and Inspection of Viruses, Serums, Toxins and Analogous Products Intended for Use in the Treatment of Domestic Animals, Regulation 1	Viruses, serums, toxins, and analogous products shall include all viruses, serums, toxins, and analogous products intended for use in the treatment of domestic animals. Among such analogous products are antitoxins, vaccines, tuberculins, malleins, microorganisms, killed microorganisms, and products of microorganisms.
1919 U.S. Department of Agriculture, Bureau of Animal Industry – BAI Order No. 265, Regulations Governing the Participation, Sale, Barter, Exchange, Shipment and Inspection of Viruses, Serums, Toxins and Analogous Products Intended for Use in the Treatment of Domestic Animals, Regulation 1, ¶3	Viruses, serums, toxins, and analogous products ~~shall include all~~ **or veterinary biologics: All** viruses, serums, toxins, and analogous products~~ intended for use in the treatment of domestic animals. Among such analogous products are~~**, such as** antitoxins, vaccines, tuberculins, malleins, microorganisms, killed microorganisms, and products of microorganisms **which are intended for use in the treatment of domestic animals**.
1922 U.S. Department of Agriculture, Bureau of Animal Industry – BAI Order No. 276, Regulations Governing the Participation, Sale, Barter, Exchange, Shipment and Inspection of Viruses, Serums, Toxins and Analogous Products Intended for Use in the Treatment of Domestic Animals, Regulation 1, ¶3	Viruses, serums, toxins, and analogous products, or veterinary biologics: All viruses, serums, toxins, and analogous products, such as antitoxins, vaccines, tuberculins, malleins, **live** microorganisms, killed microorganisms, **or bacterins,** and products of microorganisms which are intended for use in the treatment of domestic animals.
1948 9 CFR § 101.1(c) (13 Fed. Reg. 9296, 9296)	~~Viruses, serums, toxins, and analogous products, or veterinary biologics.~~ All viruses, serums, toxins, and analogous products, such as antitoxins, vaccines, tuberculins, malleins, live microorganisms, killed microorganisms, ~~or bacterins,~~ and products of microorganisms ~~which are~~**,** intended for use in the treatment of domestic animals**, including the diagnosis or detection of diseases of such animals**.
1968 9 C.F.R. § 101.1(c) (33 Fed. Reg. 3104, 3104)	All viruses, serums, toxins, and analogous products **of natural or synthetic origin**, such as antitoxins, vaccines, tuberculins, malleins, live ~~microorganisms, killed microorganisms, and products of microorganisms~~ **micro-organisms, killed micro-organisms, and the antigenic or immunizing components of micro-organisms**, intended for use in the treatment of domestic animals, including the diagnosis or detection of diseases of such animals.
1973 9 CFR § 101.2(w) (38 Fed. Reg. 8426, 8427)	All viruses, serums, toxins, and analogous products of natural or synthetic origin, such as **diagnostics,** antitoxins, vaccines, ~~tuberculins, malleins,~~ live micro-organisms, ~~killed micro-organisms,~~ and the antigenic or immunizing components of micro-organisms, intended for use in the ~~treatment of domestic animals, including the~~ diagnosis**, treatment,** or ~~detection~~ **prevention** of diseases of ~~such~~ animals.

DATE/SOURCE	VETERINARY REGULATORY LANGUAGE
1997 9 CFR § 101.2 (62 Fed. Reg. 31326, 31328)	All viruses, serums, toxins~~, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live micro-organisms, and the~~ **(excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The term "biological products" includes but is not limited to vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines,** antigenic or immunizing components of ~~micro-organisms, intended for use in the diagnosis, treatment, or prevention~~ **live organisms, and diagnostic components, that are of natural or synthetic origin, or that are derived from synthesizing or altering various substances or components of substances such as micro-organisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.** **(1) A product's intended use shall be determined through an objective standard and not a subjective one, and would be dependent on factors such as representations, claims (either oral or written), packaging, labeling, or appearance.** **(2) The term analogous products shall include:** **(i) Substances, at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which are similar in function to biological products in that they act, or are intended to act, through the stimulation, supplementation, enhancement, or modulation of the immune system or immune response; or** **(ii) Substances, at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals through the detection or measurement of antigens, antibodies, nucleic acids, or immunity; or** **(iii) Substances, at any stage of production, shipment, distribution, or sale, which resemble or are represented as biological products intended for use in the treatment of animals through appearance, packaging, labeling, claims (either oral or written), representations, or through any other means.** **(3) The term "treatment" shall mean the prevention, diagnosis, management, or cure** of diseases of animals.