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Warren Glass
AN ENVIRONMENTAL & WATER RESOURCES LAW PRACTICE

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ENVIRONMENTAL QUALITY BOARD

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September 13, 2013

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IRRC
2013 SEP 18 PM 4: 19

Via Express Mail, Return Receipt Requested

Environmental Quality Board
Rachel Carson State Office Building
16th Floor
400 Market Street
Harrisburg, PA 17101-2301

Re: Proposed Rulemaking
Regulated Medical and Chemotherapeutic Waste
[25 PA. CODE CHS. 271, 272, 273, 284, 285, 287, 288 AND 299]
43 Pa.B. 4858-4890 (Aug. 24, 2013)

Dear Members of the Environmental Quality Board:

On behalf of Merck Sharp and Dohme Corp. and Sanofi Pasteur Inc. I hereby respectfully submit the following documents regarding the above-referenced proposed rulemaking published in the Pennsylvania Bulletin on August 24, 2013 at 43 Pa.B. 4858-4890:

(1) Summary of Comments of Merck Sharp and Dohme Corp. and Sanofi Pasteur Inc. on Proposed Amendments to Regulated Medical and Chemotherapeutic Waste Regulations, and

(2) Comments of Merck Sharp and Dohme Corp. and Sanofi Pasteur Inc. on Proposed Amendments to Regulated Medical and Chemotherapeutic Waste Regulations.

Very truly yours,

Kenneth J. Warren

KJW/sl

Enclosures

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Summary of Comments of Merck Sharp and Dohme Corp. and Sanofi Pasteur Inc. on Proposed Amendments to Regulated Medical and Chemotherapeutic Waste Regulations

Merck Sharp and Dohme Corp. ("Merck") and Sanofi Pasteur Inc. ("Sanofi Pasteur") submit their joint comments ("Comments") on the proposed amendments to Pennsylvania's Regulated Medical and Chemotherapeutic Waste regulations. Merck and Sanofi Pasteur operate facilities for the production and research and development ("R&D") of vaccines and other biologics ("biologics facilities") that employ more than 13,000 people within this Commonwealth. These Comments including the proposed regulatory language are designed to enhance the efficiency and effectiveness of the proposed amendments as they apply to biologics facilities.

The unique activities conducted at biologics facilities, the stringent federal regulatory programs that apply to development and production of biologics, the expertise of biologics facility scientists and the well-characterized waste streams generated at these facilities support the adoption of regulatory provisions specific to their operations. These Comments recommend the following:

1. Waste from biologics facilities that contains no biological agents classified above Biosafety Level 1 under Centers for Disease Control and Prevention and National Institutes of Health protocols should be exempted from the definition of regulated medical waste because it poses no appreciable risk of causing disease.

2. The large volume of plastics generated by biologics facilities should be exempted from the definition of "sharps" because they pose little risk of puncture and are not considered "sharps" in almost all other jurisdictions.

3. The term "residue in empty containers" should be defined by borrowing the definition in the hazardous waste regulations, thereby providing clarity and certainty.

4. The term "cell lines" should be clarified to include as regulated medical waste only those cell lines that have been exposed to an infectious agent.

5. The requirement that regulated medical waste be segregated from chemotherapeutic waste should not apply to biologics facilities that combine infectious agents and chemotherapeutic material as part of their R&D activities.

6. The disinfection, monitoring, validation and disposal requirements in the regulations should be simplified for the wastes generated at biologics manufacturing facilities that utilize expert biosafety committees and consultants.

7. The proposed amendments regarding the submission of analyses and manifesting should be adopted.

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Re: Proposed Rulemaking
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43 Pa.B. 4858-4890 (Aug. 24, 2013)

Comments of Merck Sharp and Dohme Corp. and Sanofi Pasteur Inc.

Dear Members of the Environmental Quality Board:

Merck Sharp and Dohme Corp. ("Merck") and Sanofi Pasteur Inc. ("Sanofi Pasteur") respectfully submit the following comments on the above-referenced proposed rulemaking ("Proposed Rulemaking") published in the Pennsylvania Bulletin on August 24, 2013, *see* 43 Pa.B. 4858-4890.

Merck is a global healthcare company that delivers innovative health solutions through its prescription medicines, vaccines, biologic therapies, animal health and consumer care products. Merck's vaccine products consist of preventative pediatric, adolescent and adult vaccines.[1] Merck's worldwide headquarters for production and research and development ("R&D") of vaccines is located in a 400-acre campus in West Point, PA and employs over 10,000 Pennsylvanians.

[1] Vaccines produced by Merck include, among others, measles, mumps and rubella (MMR) and Varicella vaccines, human papillomavirus quadrivalent vaccine (Gardasil), rotavirus vaccine, hepatitis B vaccine and pneumococcal vaccine.

Sanofi is an integrated global healthcare company focused on patient needs and engaged in the research, manufacture and marketing of healthcare products. The Sanofi group of companies is organized around three principal activities: pharmaceutical, human vaccines and animal health. Sanofi's vaccines division, Sanofi Pasteur, manufactures a range of vaccines administered to children, adolescents and adults.[2] Sanofi's headquarters in the United States for production of vaccines is located in Swiftwater, Pennsylvania and employs approximately 3,000 Pennsylvanians.

The broad range of vaccines manufactured at these Pennsylvania facilities are distributed world-wide and are critical for human health.[3] The Department is well acquainted with both of these facilities as a result of the waste, water and air permits issued for their operations. Pennsylvania also hosts several other large facilities owned by other companies with similar operations. Throughout these comments, facilities engaged in the R&D and/or production of vaccines and other biologics will be referred to as "biologics facilities."[4] A summary of the comments is provided, followed by a more detailed discussion.

Pennsylvania's current Infectious and Chemotherapeutic Waste ("ICW") regulations establish a program to manage ICW throughout the Commonwealth. The objective of the ICW regulations is to avoid disease or other injury to human health or the environment that may result from exposure to ICW. Because hospitals, clinics, doctors' offices and other medical facilities generate similar waste streams, the ICW regulations impose a single set of standards and requirements applicable to all facilities. This uniform approach works well when the generators are not subject to separate, intensive federal requirements and protocols and when the quantity and types of waste do not warrant expending resources to distinguish among degrees of risk posed by components of the waste.

In contrast, the approach of the existing ICW regulations and the proposed amendments does not take into account the stringent regulations, protocols and industry standards that apply to the activities at biologics facilities. The unique characteristics of vaccine and biologics R&D and production activities present the Department with the opportunity to tailor infectious waste

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[2] Vaccines produced by Sanofi Pasteur include, among others, seasonal influenza vaccines, inactivated poliomyelitis vaccines, pediatric combination vaccines, adult and adolescent booster vaccines, mengiococcal vaccines and travel and endemics vaccines.

[3] Many of the vaccines manufactured in Pennsylvania are administered to children world-wide to prevent measles, mumps, rubella, varicella (chicken pox) and other childhood illnesses. Pennsylvania facilities are the sole source of other vaccines that control life-threatening diseases endemic to developing countries.

[4] Regulations promulgated by the U.S. Food and Drug Administration ("FDA") define a biologic (also termed a "biological product") as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of disease or injuries of man...." 21 C.F.R. § 600.3(h). Vaccines are therefore one type of biological product. Biologics facilities can be identified by reference to the North American Industrial Classification System (NAICS) which classifies "Biological Product (except Diagnostic) Manufacturing" as Code 325414 and "Research and Development in Biotechnology" as Code 51477.

requirements to enhance the efficiency and effectiveness of the regulations and reduce regulatory burdens without posing additional risk. In light of the large quantities of waste generated at biologics facilities and the substantial expense in managing the waste under the ICW regulations, it is imperative to carefully tailor the regulations to address any actual risks to the public or environment.

Biologics facilities are highly regulated by the U.S. Food and Drug Administration ("FDA"), which imposes stringent requirements and mandates practices to ensure the purity and safety of vaccine products. *See*, Comment I.B. *infra*. Following FDA procedures, researchers and manufacturers have attenuated (weakened) or inactivated vaccine viruses to reduce their hazard while maintaining their efficacy in preventing disease.

In addition to complying with FDA regulations, biologics facilities adhere to well-established risk management protocols. Biologics facilities assiduously follow the Centers for Disease Control and Prevention's ("CDC") biosafety guidelines which require companies to classify infectious agents present at their facilities into one of four biosafety levels based on the risk that the agents pose. The biosafety level dictates the extent of precautions that must be taken to protect employees and the environment from exposure to viral and other agents. Pursuant to CDC requirements, qualified personnel at biologics facilities assign to each attenuated or inactivated virus or other biologic a biosafety level based on evaluation of the risk posed. Biosafety Level 1 agents are those that do not pose a risk of disease requiring special precautions or handling. The careful risk evaluation process conducted at biologics facilities creates a substantial basis for imposing ordinary municipal or residual waste management requirements on infectious (regulated medical) wastes containing only Biosafety Level 1 agents.

The consequences of applying the current "one size fits all" regulations to biologics R&D and production wastes are severe. Biologics manufacturers produce ICW in much larger quantities than do other generators. For example, in one manufacturing process alone, Merck generates approximately 12,000 plastic roller bottles (one-liter size) per week that were used to grow vaccine viruses. FDA requirements to guarantee sterility of vaccines mandate that these bottles be used only once. Most of the bottles hold only Biosafety Level 1 agents and therefore do not pose a risk of disease requiring special precautions or handling. Disposing of these bottles as ICW costs Merck over $2 million a year. This cost is not incurred by vaccine manufacturers in other states that regulate ICW more precisely. These states impose ICW requirements only on those waste streams from biologics facilities that pose risk to the public.

In developing the current proposed amendments to the ICW regulations, the Department did not solicit or receive input from vaccine manufacturers. Even so, there are, as detailed in Comment VII below, several proposed amendments important to biologics companies that Merck and Sanofi Pasteur support. Nevertheless, the proposed amendments are unnecessarily burdensome to biologics companies in other respects. Merck and Sanofi Pasteur respectfully submit these comments to bring to the Department's and the Environmental Quality Board's attention the concerns and suggestions specific to vaccine and other biologic operations. For the reasons discussed in Comment I below, Merck and Sanofi Pasteur request that Pennsylvania's ICW regulations be amended to exclude wastes containing only Biosafety Level 1 agents generated by biologics facilities from the purview of the ICW regulations. For the reasons discussed in Comments II through VI below, Merck and Sanofi Pasteur request that the ICW

regulations be further amended to exclude plasticware used at biologics facilities from the definition of sharps, to more precisely define the exemption for "residue in empty containers" as it applies to vaccine and other biologic production and R&D wastes, to clarify that "cell lines" used at biologics facilities are not subject to ICW requirements unless they are exposed to an infectious agent, to provide that ICW that is generated at biologics facilities need not be segregated, and to simplify disinfection processing, monitoring and validation and waste management and disposal requirements for waste from the production of vaccines and other biologics.

I. Wastes Generated at Vaccine or Other Biologics Facilities That Contain Only Biosafety Level 1 Agents Should Be Included Among the Exemptions to the Definition of Regulated Medical Waste in the ICW Regulations.

A. Under Pennsylvania's Current ICW Regulations, Most Production and R&D Wastes Generated at Biologics Facilities are Handled as ICW.

The activities conducted at biologics facilities generate large quantities of materials that cannot be reused under applicable FDA regulations. These materials include, among others, cultures, containers and other wastes that have come into contact with vaccine viruses.[5] Accordingly, waste storage, handling and disposal pose important operational challenges.

In Pennsylvania, the ICW regulations provide the principal requirements governing management of ICW. In pertinent part, the ICW regulations define "infectious waste" (proposed to be changed to "regulated medical waste") as follows:

> *Infectious waste –*
>
> *(i) General.* Municipal and residual waste which is generated in the diagnosis, treatment, immunization or autopsy of human beings or animals, in research pertaining thereto, in the preparation of human or animal remains for interment or cremation, or in the production or testing of biologicals, and which falls under one or more of the following categories:
>
> (A) *Cultures and stocks.* Cultures and stocks of infectious agents and associated biologicals, including the following: cultures from medical and pathological laboratories; cultures and stocks of infectious agents from research and industrial laboratories; wastes from the production of biologicals; discarded live and attenuated vaccines except for residue in emptied containers; and culture dishes, assemblies and devices used to conduct diagnostic tests or to transfer, inoculate and mix cultures. . . .

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[5] More technically, vaccine components have been described as "live attenuated preparations of viruses, inactivated whole or subunit virions, purified recombinant proteins, synthetic antigens or live viral vectors expressing specific heterologous antigens." FDA, *Guidance for Industry, Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications* (Feb. 2010) ("FDA Guidance") at p. 2.

(ii) Mixtures. ...

(A) The term also includes mixtures of materials identified in subparagraph (i) that are mixed with municipal and residual waste, including disposable containers."

25 Pa. Code § 271.1. In turn, the ICW regulations define an "infectious agent" as "an organism, such as a virus or bacteria, that is capable of being communicated by invasion and multiplication in body tissues and *capable of causing disease or adverse health impacts in humans.*" *Id.* (emphasis added).

The definitions recognize the intent of the regulations to protect against adverse health effects by including in the definition of "infectious agent" the phrase "capable of causing disease or adverse health impacts in humans." As discussed in greater detail below, in interpreting similar language in their own regulations, EPA and some states have excluded from the definition of "cultures and stocks" those materials that do not pose an appreciable risk of causing disease, including materials classified as Biosafety Level 1. In contrast, the Department has interpreted Pennsylvania's ICW regulations to classify as ICW all cultures and equipment that have come into contact with a live or attenuated vaccine virus even where that material poses minimal risk to human health or the environment. To comply with the broad reading that the Department has given to this definition to date, biologics facilities have handled and disposed of many non-disease causing biologicals and their containers as ICW. As a result, these biologicals and their containers are segregated, packaged according to ICW requirements and incinerated or otherwise processed or disposed at facilities authorized to accept ICW, even though the vast majority of this waste poses no appreciable risk of causing disease or other adverse human health effects.

B. Due to FDA Regulations and Oversight and Adherence to Protocols Set Forth in Federal Guidelines, Wastes Generated at Biologics Facilities and Containing Only Biosafety Level 1 Vaccine Strains or Other Level 1 Biological Materials Should Be Added to the List of Exemptions from ICW Requirements.

Vaccines are a category of drugs under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §301 et seq. As a result, biologics facilities are subject to intensive regulation by the FDA to ensure the purity and safety of their products. Vaccine viruses must be free of microorganisms that may be inadvertently introduced in their production (adventitious agents). *See* 21 C.F.R. §§ 610.13 and 600.3(r). Cultures must be stored in a manner to protect them from contamination and deterioration. 21 C.F.R. § 610.18(a). Cultures are tested for the presence of microbial agents and as otherwise required to ensure the safety, purity and potency of the product. 21 C.F.R. § 610. Comprehensive testing and qualification of the biological materials and lot-by-lot testing for adventitious agents are conducted. *See* FDA Guidance at 3. Current Good Manufacturing Practices (cGMP) as set forth in 21 C.F.R. Parts 211, 600-680 and 1271 are rigorously followed. These practices control the risk that the production and handling of materials will allow introduction of unwanted infectious agents into a vaccine or other biologic.

Improvements in practices and technology have also increased the safety of vaccine viruses. In recent years, many vaccine agents that were once infectious have been attenuated to the point that they are not capable of being communicated by replication or invasion in healthy humans. *See, e.g.*, J. Cohen, *Varicella-Zoster Vaccine Virus: Evolution in Action*, 104 PNAS

No. 1 at pp. 7-8. Through application of its scientific and medical expertise, the vaccine industry has been successful in reducing risk from the viruses themselves. This in turn reduces the need to impose the additional protections afforded by the ICW regulations when containers and other wastes that have come into contact with the biologics are disposed.

Vaccine manufacturers assess the hazards of the vaccine viruses and other infectious agents and biological materials that they research, develop and produce based upon established protocols recognized by the federal and some state environmental agencies. In regulations promulgated by EPA pursuant to the Medical Waste Tracking Act of 1988, EPA excluded from the definition of medical waste various waste types listed in section 11002(a) of RCRA that "do not pose a substantial present or potential hazard to human health or the environment when improperly managed." 54 Fed. Reg. 12326, 12342 (March 24, 1989). The classes of medical wastes identified for tracking under the program included cultures and stocks *of infectious agents and biologicals*, 42 U.S.C. §6992a, a category described in statutory language similar to that adopted by Pennsylvania. Under EPA regulations implementing the Medical Waste Tracking Act, like the ICW regulations in Pennsylvania, an "infectious agent" must be "capable of causing disease or adverse health impacts in humans." 40 C.F.R. § 259.10. As EPA explained in the preamble to these regulations, under this definition not all viruses and biologicals should be considered "infectious agents":

> As guidance in determining what "infectious agents" are, those agents listed in Classes 2 through 4 of the *Centers for Disease Control's (CDC's) Classification of Etiologic Agents on the Basis of Hazard* (July 1974) would be included. EPA believes that these guidelines are suitable to indicate which medical wastes warrant regulation.

54 Fed. Reg. 12326, 12340.[6]

In other words, EPA considers only Classes 2 through 4 agents, not Class 1 agents, as "infectious agents" covered by the regulations. The July 1974 CDC guidance cited by EPA defines Class 1 agents as "agents of no or minimal hazard under ordinary conditions of handling." Unlike waste containing agents in Classes 2 through 4, wastes containing agents classified under CDC protocols as Class 1 are not considered capable of causing disease in humans and do not warrant regulation as ICW.

Since issuing the version of the 1974 CDC guidance cited in EPA's preamble, CDC has revised its definitions from Class 1 through 4 agents to Biosafety Levels 1 through 4 agents as currently reflected in CDC's *Biosafety in Microbial and Biomedical Laboratories* (BMBL) (5th 2009). The CDC defines BSL-1 as "the basic level of protection and is appropriate for agents that are not known to cause disease in normal, healthy humans." *Id.* at p. 4. This is equivalent to the former Class 1. The CDC classifications are closely observed at biologics

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[6] EPA apparently concluded that only wastes exposed to Classes 2 through 4 agents fall within the ambit of its regulatory program without considering the additional reasons why vaccine manufacturing wastes containing only Class 1 organisms pose even less risk than ICW from medical facilities. Table 1 to the EPA regulations listing the quantity of waste generated by various categories of generators and Table 2 summarizing annual costs of compliance do not mention vaccine or other biologic manufacturers.

facilities in selecting the procedures and protections necessary to safeguard their own employees and the environment. As the CDC has recognized, the BMBL is "the cornerstone of biosafety practice and policy in the United States." *Id.* at p. iii. The CDC classifications remain the best indicator of the level of regulation necessary to protect the public from exposure to waste containing biological agents.

As the CDC BMBL notes, the biosafety levels correlate with the risk group classifications established by the National Institutes of Health ("NIH") in its *Guidelines for Research Involving Recombinant DNA Molecules* (April 2002) ("*NIH Guidelines*") and the World Health Organization ("WHO") in its *Laboratory Biosafety Manual* (3rd ed. 2004). NIH defines Risk Group 1 agents as those agents "not associated with disease in healthy adult humans." *NIH Guidelines* at p. 12. Under the NIH approach, in deciding on the appropriate containment required for an agent, the first step is to assess the risk of the agent itself. *Id.* at p. 13. Various agents are listed in Appendix B to the *NIH Guidelines* based upon their risk group. However, NIH accounts for advances in the development of vaccine strains that pose less risk than the parent strain. The *NIH Guidelines* state:

> Certain attenuated strains or strains that have been demonstrated to have irreversibly lost known virulence factors may qualify for a reduction of the containment level compared to the Risk Group assigned to the parent strain.

Id. at p. 13. This reduction of risk has occurred by engineering modern vaccine viruses. For example, some viral strains have ejected the genomic information to produce disease and can only replicate under the growth conditions present at biologics facilities and not in humans.

NIH has established rigorous procedures for classifying biological agents that are followed by institutions conducting or sponsoring recombinant or synthetic nucleic acid molecule research.[7] Companies subject to the *NIH Guidelines* must establish an Institutional Biosafety Committee with members having experience and expertise in recombinant or synthetic nucleic acid molecule technology. The members must have the capability to assess the safety of the research conducted at the facility and to identify any potential risk to public health or the environment. *Id.* at pp. 24-26. The Institutional Biosafety Committee is responsible for, among other things, conducting an independent assessment of the containment levels required. *Id.* at 27. An institution engaging in large-scale R&D or production activities involving viable organisms containing recombinant or synthetic nucleic acid molecules must also appoint a Biological Safety Officer ("BSO") to, among other things, provide advice to the Institutional Biosafety Committee. *Id.* at 28. The expertise of the Biosafety Committee and the BSO ensures that risk classifications are properly made.

Similarly, the WHO states that infectious agents classified as Risk Group 1 are those "unlikely to cause human or animal disease." WHO, *Laboratory Biosafety Manual*, supra at 1. Professional judgment is then exercised through a risk assessment to assign biosafety levels. *Id.*

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[7] The NIH Guidelines are broadly applicable to recombinant or synthetic nucleic acid research within the United States. NIH Guidelines at pp. 10-11. In many instances, compliance is mandatory: "As a condition for NIH funding of recombinant or synthetic nucleic acid molecule research, institutions shall ensure that such research conducted at or sponsored by the institution, irrespective of the source of funding, shall comply with the NIH Guidelines." *Id.* at p. 11.

at 3. The WHO has recognized that Biosafety Level 1 agents are safe and not infectious: "Historical evidence indicates that microorganisms handled at this level are unlikely to cause human disease or animal disease of veterinary importance." *Id.* at 16. No safety equipment is required to handle Biosafety Level 1 materials. *Id.* at 2, Table 2. Designation of a qualified biosafety officer and formation and use of a biosafety committee with responsibilities similar to those specified by NIH is recommended. *Id.* at 117-118.

The New York State Department of Health has joined the federal government in referencing biosafety levels when interpreting the category of medical wastes that includes "cultures and stocks of agents infectious to humans." The N.Y. Department of Health Guidelines for managing regulated medical waste state:

> The key to this subcategory [cultures and stocks] is understanding what is meant by agents infectious to humans. The department has identified that such agents are currently described in Section 2.1 of the State Sanitary Code as those causing communicable diseases (Attachment 1). Those guidelines also recommend the inclusion within this subcategory of those agents designated as requiring biosafety level II-IV in the *CDC/NIH Manual for Biosafety in Microbiological and Biomedical Laboratories.*
>
> NYS Department of Health, Guidelines under Public Health Law 1589.[8]

Merck and Sanofi Pasteur have established biological risk management programs to comply with all applicable local, state and national regulatory requirements and applicable consensus standards. These programs require the establishment of biosafety committees with members possessing the expertise and experience to evaluate the implementation and effectiveness of their respective risk management programs. The programs require maintenance of an inventory of biological agents denoting, among other things, the risk group into which the agent falls. Merck and Sanofi Pasteur also instruct their respective facilities to conduct a biological risk assessment for all activities involving the handling, storage and disposal of biological materials, including an assessment of human and environmental risks. These

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[8] Virginia likewise characterizes regulated medical waste as waste pathogenic to healthy humans: "9VAC20-120-140. Characteristics of regulated medical waste.

A solid waste is a regulated medical waste if it meets either of the two criteria of this section:

1. Any solid waste, as defined in this chapter is a regulated medical waste if it is suspected by the health care professional in charge of being capable of producing an infectious disease in humans. A solid waste shall be considered to be capable of producing an infectious disease if it has been or is likely to have been contaminated by an organism likely to be pathogenic to healthy humans, such organism is not routinely and freely available in the community, and if such organism has a significant probability of being present in sufficient quantities and with sufficient virulence to transmit disease. If the exact cause of a patient's illness is unknown, but the health care professional in charge suspects a contagious disease is the cause, the likelihood of pathogen transmission shall be assessed based on the pathogen suspected of being the cause of the illness.
2. Any solid waste that is not excluded from regulation is a regulated medical waste if it is listed in 9VAC20-120-150."

sophisticated programs relying on expert biosafety committees ensure that infectious agents at biologics facilities are properly classified. Wastes containing only Biosafety Level 1 agents do not require regulation as ICW.

RECOMMENDATION:

Based on the foregoing, Merck and Sanofi Pasteur recommend that the following regulatory amendments be adopted:

25 Pa. Code § 271.1 is amended to add the following language to the definition of "infectious waste" (to be changed to "regulated medical waste"):

(iii) Exemptions: The term does not include the following:

. . . (L) Wastes or mixtures of wastes from facilities engaged in the production or research and development of vaccines or other biologics and classified under the North American Industrial Classification System (NAICS) as Code 325414 - Biological Product (except Diagnostic) Manufacturing or Code 541711 - Research and Development in Biotechnology, where no agent in the waste is classified as Biosafety Level 2-4 as determined by the protocols established in the most recent edition of the Centers for Disease Control's *Biosafety in Microbial and Biomedical Laboratories* (BMBL) existing at the time the waste is generated.

and

25 Pa. Code § 271.1 is amended to add the following language to the definition of "infectious agent":

An organism, such as a virus or bacteria, that is capable of being communicated by invasion and multiplication in body tissues and capable of causing disease or adverse health impacts in humans. **The term does not include agents classified as Biosafety Level 1 by a facility engaged in the production or research and development of vaccines or other biologics classified under the North American Industrial Classification System (NAICS) as Code 325414 - Biological Product (except Diagnostic) Manufacturing or Code 541711 - Research and Development in Biotechnology.**

II. Plasticware Should Not Be Included in the Definition of Sharps.

The ICW regulations establish requirements for the management of used sharps that do not apply to other categories of ICW. *See, e.g.*, 25 Pa. Code §§ 284.412 (sorting), 284.415 (storage containers), 284.16 (markings), and 284.512 (transportation). Vaccine manufacturers generate large quantities of plastic bottles, tubing and other materials that pose little risk of puncture. Handling these plastic materials as sharps poses an unnecessary expense and burden on vaccine activities in Pennsylvania.

The definition of "sharps" set forth in 25 Pa. Code § 271.1 includes "broken or unbroken glass or plasticware."[9] The proposed amendments to the definition of sharps do not remove plasticware from the definition of sharps.[10] Besides Pennsylvania, we have been able to identify only a handful of other states that define sharps to include plasticware.[11] The other states do not. There is a simple explanation for the decision of the vast majority of jurisdictions: plasticware does not present a significant risk of puncturing skin as do needles and glassware and therefore does not require the same degree of regulation.

In its regulations implementing the Medical Waste Tracking Act, EPA defined sharps as follows:

> Sharps that have been used in animal or human patient care or treatment or in medical, research, or industrial laboratories, including hypodermic needles, syringes (with or without the attached needle), pasteur pipettes, scalpel blades, blood vials, test tubes, needles with attached tubing, and culture dishes (regardless of presence of infectious agents). Also included are other types of broken or

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[9] Sharps are defined as: "Broken glass that has been in contact with pathogenic organisms, hypodermic needles and syringes to which a needle can be attached, with or without the attached needle, suture needles, disposable razors, pasteur pipettes, scalpel blades, blood vials, needles with attached tubing, culture dishes, suture needles, slides, cover slips and other broken or unbroken glass or plasticware." 25 Pa. Code § 271.1. Used sharps are a category of "infectious waste" and are defined as follows: "Sharps that have been in contact with infectious agents or that have been used in animal or human patient care or treatment, at medical, research or industrial laboratories." *Id.*

[10] As proposed in the amendments to the ICW regulations, "sharps" would be defined as follows: "Broken glass, hypodermic needles, syringes to which a needle is or can be attached, razors, Pasteur pipettes, scalpel blades, blood vials, needles with attached tubing, culture dishes, suture needles, slides, cover slips and other broken or unbroken glass or plasticware." As proposed in the amendments to the ICW regulations, "used sharps" would be defined as follows: "Sharps that have been in contact with infectious agents or that have been used in animal or human patient care or treatment."

[11] Of these states, only New York and New Mexico include all varieties of unbroken plasticware in their definition. *See* 10 NYCRR § 70-1.2; 20.9.2.7 NMAC. Minnesota only includes one variety of unbroken plasticware, "rigid plastic vials," in its definition. Minn. R. 7035.9110. Ohio defines the term "Sharp objects" to include "hard plastic." OAC Ann. 3745-27-01. Massachusetts only includes broken plasticware in its definition. *See* 105 CMR 480.010. Maryland only includes one variety of broken plasticware, "broken rigid plastic," in its definition. COMAR 26.13.11.02. And Wisconsin narrows that variety of broken plasticware still further, including only "broken rigid plastic vials" in its definition. Wis. Adm. Code NR 526.05. Some examples of nearby states that do not reference plasticware at all in their definitions of sharps include: New Jersey (N.J.A.C. 7:26-3A.6); Delaware (CDR 7-1000-1301); Connecticut (Regs., Conn. State Agencies § 22a-209-15); Rhode Island (CRIR 12-030-017); and Virginia (9 VAC 20-120-10).

> unbroken glassware that were in contact with infectious agents, such as used slides and cover slips.[12]

Plasticware is not included in the definition. Likewise, the U.S. Occupational Safety and Health Administration (OSHA) does not include plasticware in its definition of "contaminated sharps" in the bloodborne pathogen standard.[13]

The preamble to the 1992 regulatory package containing Pennsylvania's then proposed ICW regulations notes that the proposal "borrows from the Federal definition of medical waste, and includes some of the Federal storage and transportation requirements." 22 Pa. B. 4185 (August 8, 1992). Nevertheless, in this instance without discussion, the final Pennsylvania regulations deviated from the federal definition and place this Commonwealth in the present company of only a handful of other jurisdictions that include plasticware as sharps.

In 1993, the Department provided additional guidance for determining which plastics constitute sharps. The guidance states:

> Infectious waste - (F)
>
> Used sharps:
>
> > Category (F) requires that broken and unbroken glass and plastic ware that have been in contact with infectious agents or used in animal or human patient care or treatment be managed as infectious waste. The term "plastic ware" is to be interpreted to mean items made from plastic polymers which shatter on breakage or would be considered breakable, thus creating sharps capable of skin punctures in those who may come in contact with them. If used "plastic ware" is made of a plastic polymer which does not shatter on breakage or is considered unbreakable, it would not be considered a used sharp. However, this "plastic ware" would still be required to be managed as infectious waste if through its use it has been in contact with infectious agents. Therefore, rinsing glass or plastic containers, used for specimens of blood or body fluids, does not overcome their management as infectious waste.

PADEP Guidance Document No. 254-2167-726, "Infectious Waste Definition Clarification of Human and Animal Blood and other Bodily Fluid Waste" (November 10, 1993).

On its face, the "breakable/unbreakable" distinction in this guidance would appear to address the concern of vaccine manufacturers regarding the applicability of the "used sharp" requirements of the regulations: the large quantities of plastic bottles and tubing generated at vaccine facilities are not breakable under real world conditions. Department staff, however, has

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[12] 40 C.F.R. § 259.51 (Table-Regulated Medical Waste). The regulatory definition expands the statutory language: "Sharps that have been used in patient care or in medical, research or industrial laboratories, including hypodermic needles, syringes, pasteur pipettes, broken glass, and scalpel blades." 42 U.S.C. § 6992a(a)(4).

[13] "Contaminated Sharps means any contaminated object that can penetrate the skin including, but not limited to, needles, scalpels, broken glass, broken capillary tubes, and exposed ends of dental wires." 29 C.F.R. §1910.1030(b).

read the guidance to include within the definition of used sharps those plastics that can break or shatter only under conditions which are unlikely to occur.[14] Because used sharps are a category of ICW, the current interpretation has caused vaccine manufacturers to needlessly expend resources to manage, transport and dispose of large quantities of plastic bottles and other plastics as sharps even though they are engineered to avoid breakage except under extreme conditions.

The Preamble to the current proposed amendments to the ICW regulations, like the 1992 Preamble, expresses the intent to conform Pennsylvania requirements to those used nationally. As stated in the current Preamble:

> Since solid waste is not always generated, processed and disposed of within this Commonwealth, the proposed revisions allow persons generating and managing infectious and chemotherapeutic waste to do so in a manner that complies with Commonwealth law and is consistent with Federal requirements and the requirements of other states....
>
> This uniform practice should reduce the costs borne by generators and other persons managing regulated medical waste....
>
> [The elimination of provisions that relate to areas governed by OSHA] removes the possibility that provisions may be inconsistent or duplicative of OSHA requirements but in no way affects the applicability of OSHA requirements to persons within this Commonwealth.

Proposed Rulemaking, 43 Pa. B. 4858-59 (Aug. 24, 2013).

We applaud the Department's efforts to achieve consistency. Consistent rules among states governing wastes from biologics facilities is extremely important to our businesses to ensure that additional regulatory burden in this Commonwealth does not put us at a competitive disadvantage to facilities in neighboring states. Notwithstanding its objective, the Department has chosen to define sharps in a more stringent manner than other neighboring states.

Some of the concerns addressed in this section could be alleviated if the regulations were clarified to exclude from the definition of infectious waste (regulated medical waste) those wastes from biologics facilities that contain agents that are classified as Biosafety Level 1. By excluding those wastes from the definition of infectious wastes, they no longer fall within any subcategory of infectious waste, including subcategory F (used sharps). Nevertheless, ambiguity may still exist. In light of current Department interpretations and vaccine manufacturers' compliance, the current definitions of sharps and used sharps are creating considerable burdens. The substantial quantity of 1-liter plastic bottles generated at Merck is a poignant example of a waste stream unnecessarily regulated as sharps. These plastics pose little risk of causing injury.

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[14] Similarly, the language of the definition of "used sharps" in the current ICW regulations restricting that category to sharps "at medical, research or industrial laboratories" would appear to cover R&D but not manufacturing facilities. Once again, the Department considers plasticware from manufacturing facilities within the definition. In any event, the proposed amendments would eliminate the words "at medical, research or industrial laboratories" from the definition.

RECOMMENDATION:

Merck and Sanofi Pasteur recommend that an exemption for plasticware generated at biologics facilities be added to the definition of "used sharps," or alternatively that the definition of "sharps" be modified to exclude references to plasticware.

Alternative 1 – Add the following language to the proposed definition of "Used Sharps" found in subsection (F) to the definition of "Infectious waste" in 25 Pa. Code § 271.1: "Used sharps shall not include broken or unbroken plasticware generated at facilities engaged in the production or research and development of vaccines or other biologics and classified under the North American Industrial Classification System (NAICS) as Code 32514 - Biological Product (except Diagnostic) Manufacturing or Code 541711 - Research and Development in Biotechnology."

Alternative 2 – Modify the proposed definition of sharps to read as follows: "Sharps – Broken glass, hypodermic needles, syringes to which a needle is or can be attached, razors, Pasteur pipettes, scalpel blades, blood vials, needles with attached tubing, **glass** culture dishes, suture needles, **glass** slides, **glass** cover slips, and other broken or unbroken glass **[or plasticware]**.

III. The Department Should Define and Exempt Empty Containers Containing Residue of Wastes Generated by Biologics Facilities

The current definition of infectious waste as it pertains to cultures and stocks includes a category that reads as follows: "discarded live and attenuated vaccines except for residue in emptied containers." 25 Pa. Code §271.1. This exception for residue lacks clarity in two respects. First, it is unclear whether the exception modifies only the phrase "discarded live and attenuated vaccines" or whether the exception applies more broadly to other categories of cultures and stocks, including the category of "wastes from the production of biologicals." The more limited interpretation would appear to eliminate the exception as to vaccine manufacturing wastes because all discarded vaccines remaining in emptied containers would continue to be separately regulated as "wastes from the production of biologicals." Yet where the vaccines or other biologicals do not cause the wastes to be classified as infectious, no other basis exists to believe that the wastes from the production of biologicals may cause disease.

Second, the term "residue in emptied containers" is not defined. The absence of a clear standard leaves biologics facilities at risk that their evaluation of whether a container has been sufficiently "emptied" to trigger the exemption will differ from the Department's evaluation. Other regulatory programs define an empty container more precisely. For example, the regulations adopted under the Resource Conservation and Recovery Act ("RCRA") contain specific quantitative limits that can be used to determine whether a container is empty. 40 C.F.R. § 261.7(b)(1). The term "RCRA empty" is often used to refer to a container that is empty as defined in § 261.7 and therefore no longer subject to hazardous waste requirements. This regulation is among those incorporated into Pennsylvania's hazardous waste regulations. 25 Pa.

Code § 261.a.1.[15] Although the biologics wastes subject to the ICW regulations are not classified as hazardous wastes under RCRA, the regulated community has considerable experience applying RCRA hazardous waste requirements in other contexts. Therefore, in order to provide the clarity necessary for operators of biologics facilities to understand and fulfill their environmental obligations, we request that Pennsylvania incorporate the RCRA definition of empty containers into the ICW regulations.

RECOMMENDATION:

Based on the foregoing, Merck and Sanofi Pasteur recommend that the following regulatory amendment be adopted:

> 25 Pa. Code § 271.1 is amended to add the following language to the definition of "infectious waste" (to be changed to "regulated medical waste"):
>
> (iii) *Exemptions*: The term does not include the following:
>
> . . . (M) Wastes or mixtures of wastes from facilities engaged in the production or research and development of vaccines or other biologics, and classified under the North American Industrial Classification System (NAICS) as Code 325414 - Biological Product (except Diagnostic) Manufacturing or Code 541711 - Research and Development in Biotechnology, that consist of empty containers as determined by applying the criteria in 40 CFR § 261.7 (b)(1) or (2) to regulated medical waste remaining in the container.

IV. The Department Should Clarify That Only Cell Lines That Have Been Exposed to Infectious Agents Need To Be Regulated as ICW

General Permit No. WMGI005 approves the processing of infectious waste generated in the production and research and development of pharmaceuticals when chemical and/or thermal inactivation is used. Among the types of wastes that the operator of the permitted facility may process are "cell lines from humans and primates." Permit No. WMGI005 at p. 2. Cell lines are not capable of causing disease unless they are exposed to infectious agents. Neither the category of "cultures and stocks" nor any other category within the definition of infectious waste expressly mentions cell lines. Only cultures and stocks "of infectious agents and associated biologicals" fall within the definition of infectious waste because only those materials are capable of causing disease. The inclusion of cell lines in the general permit creates ambiguity regarding whether a cell line that has not been exposed to an infectious agent must be processed as infectious waste under the general permit.

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[15] Residue removed from a container remains subject to regulation as a hazardous waste. 25 Pa. Code § 261.a.7.

RECOMMENDATION:

Based on the foregoing, Merck and Sanofi Pasteur recommend that the following regulatory amendment be adopted:

25 Pa. Code § 271.1 is amended to add the following language to the definition of "infectious waste" (to be changed to "regulated medical waste"):

(iii) *Exemptions*: The term does not include the following:

. . . (N) Cell lines that have not been exposed to infectious agents classified as Biosafety Levels 2-4 as determined by the protocols established in the most recent edition of Centers for Disease Control's *Biosafety in Microbial and Biomedical Laboratories* (BMBL) existing at the time the waste is generated.

Alternatively, the Department may simply wish to resolve this ambiguity in the general permit by changing "cell lines from humans and primates" to "cell lines from humans and primates that have been exposed to infectious agents classified as Biosafety Levels 2-4 as determined by the protocols established in the most recent edition of Centers for Disease Control's *Biosafety in Microbial and Biomedical Laboratories* (BMBL) existing at the time the waste is generated. "

V. Biologics Facilities Should Not Be Required to Segregate Regulated Medical Waste and Chemotherapeutic Waste.

The Proposed Rulemaking would require segregation of wastes as follows:

Section 284.411 Segregation

(a) Regulated medical waste and chemotherapeutic waste shall be segregated at the point of origin at the generating facility into the following three categories:

1. Regulated medical waste, excluding pathological waste
2. Pathological waste
3. Chemotherapeutic waste

(b) Each category of waste segregated under subsection (a) shall be placed in a separate container, except used sharps that qualify as regulated medical waste may be placed in a chemotherapeutic waste sharps container.

This proposed rule does not account for the manner in which biologics facilities engaged in R&D generate waste or the safety of their on-site disposal processes. Pharmaceutical and vaccine compound research often involves the intentional combination of infectious and chemotherapeutic agents. For example, it is common practice to use a 96 well plate to test the combination of products and their targets or other cells.[16] The need to conduct research by combining infectious and chemotherapeutic agents renders it infeasible to segregate those

[16] A well plate, also known as a microtiter plate, is a flat plate with multiple "wells" or containment areas used as test tubes. The wells may be treated with tissue cultures or modified to promote cell growth. A 96 well plate arranges 96 sample wells in a rectangular matrix.

materials when discarded. If the waste is sent off-site for processing and disposal, appropriate packaging and labeling will provide sufficient protection and notice to ensure safe practices are employed.

While segregation of waste generated at biologics facilities is not feasible nor necessary generally, it is particularly unwarranted when the waste is treated or disposed onsite. For example, Merck employs an on-site incinerator and other permitted facilities to process or destroy waste. Where a biologics facility includes a captive, permitted processing facility to handle its waste, and material storage and movement is conducted entirely on-site by trained employees, the segregation of infectious and chemotherapeutic waste streams is unnecessary.

The impact of adhering to this segregation requirement would be stark. It would be impossible for biologics companies in this Commonwealth to pursue and complete their discovery of vaccines and medicines and ensure the safety of their products if this requirement were to be imposed and maintained. Exempting biologics facilities from waste segregation requirements would also result in cost savings. By allowing consolidation of wastes, fewer waste pickups would be required. In addition, the resources devoted to separating waste streams would be available for other activities.

RECOMMENDATION:

Based on the foregoing, Merck and Sanofi Pasteur recommend that the following subsection be added to the proposed amendment to § 284.411:

> (c) Facilities engaged in the production or research and development of vaccines or other biologics, and classified under the North American Industrial Classification System (NAICS) as Code 325414 - Biological Product (except Diagnostic) Manufacturing or Code 541711 - Research and Development in Biotechnology, are exempt from the requirement under subsection (a) to segregate regulated medical waste and chemotherapeutic waste.

VI. Disinfection Processing, Monitoring and Validation and Post-Disinfection Waste Management and Disposal Requirements Pertaining to Waste From the Production of Vaccines and Other Biologics Should be Simplified and Targeted to The Waste Processed.

Pennsylvania developed its existing infectious waste regulations and the proposed regulatory amendments primarily to address wastes from hospitals, clinics and other patient care facilities. These facilities use equipment that comes into direct contact with patients or blood or other bodily fluids from patients. Wastes generated by these institutions may include the full range of infectious agents to which patients have been exposed over their lifetimes, including many wild-type viruses. The medical provider has no feasible means of ascertaining the identity of each organism contained in even one patient's waste. Particularly because medical facilities combine wastes from treatment of multiple patients, there is wide variability in the waste streams, and the full range of infectious agents present in each waste stream is unknown. In response to the multiple uncharacterized infectious agents in the waste streams generated by medical providers, Pennsylvania designed its infectious waste regulations to ensure that the

disinfection process is effective for the spectrum of potential biological agents in the waste. The regulations therefore establish stringent inactivation standards and monitoring and validation testing requirements.

For example, the proposed amendments to § 284.321(a)(2) impose a standard that would protectively require certain disinfection processes such as autoclaving to be capable of inactivating mycobacteria at a 6 log 10 reduction or greater and certain bacillus spores at a 4 log 10 reduction or greater.[17] These standards are appropriately conservative when applied to the disinfection of uncharacterized infectious agents but are unnecessarily onerous when applied to the disinfection of the well-characterized waste streams from biologics facilities.

The monitoring provisions of the regulation likewise impose conservative requirements reflective of the broad array of infectious agents potentially present in the waste. When disinfection is performed by autoclaving, the amended regulations conservatively would require use of Geobacillus (currently Bacillus) stearothermophilus as an indicator to establish and verify the process. Section 284.321(d) requires the operator to perform a microbiological analysis of indicators removed from the processed waste at least every 40 hours. These criteria may be appropriate when the specific biological composition of the waste is unknown,[18] but are completely unnecessary for waste from a vaccine production process when the sole potentially infectious agent is a known, well-characterized component of a vaccine or other biologic.

The validation requirements for autoclaves are likewise aimed at ensuring that unknown biological wastes from medical providers are disinfected. Validation of the operating parameters and protocols of the autoclave equipment must be performed at least annually, and also when the autoclave is installed or modified, or when a problem or significant change in the waste stream occurs. 25 Pa. Code § 284.321(n). The specific autoclave validation testing requirements include, among other things, validating operating parameters to achieve a minimum of 250° F or 121° C measured at a point where disinfection would be most difficult to achieve. 25 Pa. Code § 284.322. Validation at a temperature of 121° C is prudent when the exact temperature at which an undetermined biological agent will be killed cannot be specified. It is overkill where the waste is known to contain only a well-characterized vaccine or other biologic that is inactivated at a much lower temperature.

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[17] The specific spores identified in the proposed amendments are Geobacillus stearothermophilus spores, Bacillus pumilus or Bacillus atrophaeus spores. § 284.321(2)(ii).

[18] There is reason to believe that these criteria may be unnecessarily burdensome even outside of the vaccine manufacturing context. Other jurisdictions such as Arkansas and Tennessee have recognized the validity of tests using chemical indicators together with periodic verification through biological indicators. *See, e.g.,* Ark 007 05 CARR 002, Sections 34 K1 and L, Tenn. Comp. R&Regs. R 0940-5-16-.15(3). The Department of Defense designates chemical indicators at locations throughout an autoclave as the primary means of verifying routine sterilization. 32 C.F.R. § 627.33. The FDA likewise recognizes the usefulness of a "physical/chemical sterilization process indicator." 21 C.F.R. § 880.2800(b). The Association for the Advancement of Medical Instrumentation has issued guidance for application of chemical indicators. ANSI/AAMI/ISO 11140-1:2005(R) 2010.

Finally, the existing regulations impose special precautions for infectious waste disposal in light of the unknown organisms that may be present in the waste. Sections 273.411 and 273.511 require Department approval for the disposal at a municipal landfill of waste disinfected in accordance with § 284.321. Ash residue from incineration of regulated medical waste must be transported separately from ash residue of other generators. 25 Pa. Code § 284.511. The inability to characterize the waste from diverse medical facilities supports imposition of special management, transportation and disposal requirements not applicable to other municipal waste streams. These requirements are unnecessary when imposed upon the well-characterized waste streams from biologics facilities.

Waste generated by manufacturers of vaccines or other biologics differs significantly from wastes generated by medical providers that serve as the focus for the regulations. As discussed in Comment I above, unlike medical providers, biologics manufacturers employ procedures mandated by governmental agencies and standard industry practices to produce well-characterized biologics free of adventitious agents. They also establish methods specific to the biological agent to effectively decontaminate any waste in contact with the agent. These procedures include:

1. Operating in accordance with FDA good manufacturing practices ("GMP") or good laboratory practices ("GLP").[19]

2. Employing trained technicians to review decontamination cycle data to confirm that kill requirements have been met.

3. Establishing and implementing maintenance and calibration programs for decontamination equipment.

4. Defining the methods and minimum parameters for biological kill of the infectious agents in the waste stream.

5. Qualifying the decontamination processes to achieve the minimum parameters for kill.

6. Implementing biosafety programs that are appropriate for the decontamination operation performed and the Biosafety Level of the infectious agents in the waste stream and that may include, among other things, practices, techniques and secondary biocontainment systems to capture any accidental discharges.

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[19] As discussed in Comment I, a central tenet of FDA requirements is that the production process for vaccines and other biologics must ensure the purity and safety of the biological product. 21 C.F.R. § 610. The environment in which vaccine viruses are grown is carefully controlled to exclude adventitious agents from the vaccine product. Consequently, in contrast to medical waste, waste generated by biologics manufacturing contains a biological agent that is well characterized and bioburden levels that are controlled, and undergoes screening for objectionable microorganisms.

7. Employing a qualified Institutional Biosafety Committee constituted in accordance with CDC/NIH guidelines and/or whose membership includes a biosafety professional certified by the American Biological Safety Association or the American Society for Microbiology, to review and approve the decontamination method for each specific infectious agent. In lieu of the Institutional Biosafety Committee a contractor with the same qualifications may be given the authority and responsibility to approve a specific decontamination.

The central role of the biologics manufacturer's Institutional Biosafety Committee in designing biosafety procedures specific to each vaccine or other biologic produced on-site results in use of sound science to establish a controlled operation and environment. The members of the committee must collectively have the experience, expertise and capability to, among other things, assess the safety of activities and identify any risk to public health or the environment. A principal function of the committee is to perform an independent assessment of the containment levels required. Understanding the risk posed by each infectious agent and how the risk may change under different conditions and over time is important to performing this function.[20]

In light of the scientific expertise and knowledge of their respective biosafety committees, Merck and Sanofi Pasteur utilize these committees to help establish or review the processes used to inactivate the biologic agent in the wastes generated at their facilities and to assess the procedures and protocols used to monitor and validate the disinfection methods and equipment. The scientific training and experience of committee members combined with their knowledge of and familiarity with the vaccine or other biologic produced at the facilities make these committees particularly well suited to establish disinfection requirements. The committees review the studies, literature, data and other documents providing the scientific justification for the decontamination processes and methods. They ascertain that use of the processes and methods will inactivate the organism in the specific vaccine or other biologic being assessed and that the monitoring and validation procedures and protocols are appropriate in light of the conditions necessary to kill the biological agent or otherwise destroy its ability to replicate.

Merck and Sanofi Pasteur propose that Pennsylvania's regulated medical waste regulations grant these expert Institutional Biosafety Committees authority and responsibility to approve the decontamination process, method and associated monitoring and validation requirements for each specific infectious agent at the facility in lieu of submitting an application to the Department for approval.

Merck and Sanofi Pasteur further propose that where the Institutional Biosafety Committee at a biologics facility determines that an outside certified contractor possesses special expertise concerning the appropriate decontamination procedures for waste from production of a specific vaccine or other biologic, the biologics manufacturer be authorized to rely on the judgment of the certified scientist who would then accept the responsibility for approval of the specific decontamination process. The American Biological Safety Association and the

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[20] These attributes and functions of the Institutional Biosafety Committee ("IBC") are set forth in the *NIH Guidelines*, *supra*, at p. 26-27. Biologics facilities that are not subject to the NIH Guidelines nonetheless utilize an IBC constituted in accordance with industry standards.

American Society for Microbiology currently offer certifications for biosafety professionals.[21] When the Institutional Biosafety Committee seeks the special expertise of a professional certified by one of these organizations, the specific disinfection requirements specified by the expert and relied upon by the biologics manufacturer should be given the same effect as requirements developed by the Committee.

Several of the suggestions made in this Section have already been put into effect by the Department through the permitting process. General Permit WMGI005 issued to Merck and Sanofi Pasteur authorizes Merck and Sanofi Pasteur to process infectious waste generated at their respective West Point, PA and Swiftwater, PA facilities in the production and research and development of pharmaceuticals using chemical and/or thermal inactivation. The permit conditions rely heavily on industry practices and standards and scientifically accepted protocols, including among others those issued by the CDC and NIH.[22]

The Institutional Biosafety Committee will make decisions utilizing established government guidelines and industry protocols as the standards for disinfection of highly-characterized manufacturing waste from vaccines and other biologics. They will also employ good science and common sense. For example, certain vaccine viruses are very sensitive to heat and must be stored in refrigerated conditions to retain their potency. When materials from the production of the vaccine virus must be disposed, the manufacturer's knowledge of how temperature changes affect the vaccine virus allows it to specify the temperature and residence time necessary to ensure the efficacy of disinfection of the wastes by autoclaving, incineration or thermal processing. There would be little purpose served by requiring validation of autoclave operating parameters at 121° C, as §284.322 now requires, if the vaccine manufacturer has demonstrated that far lower temperatures will kill the vaccine virus.

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[21] The American Biological Safety Association ("ABSA") designates an individual as a Certified Biological Safety Professional upon passage of the ABSA exam administered by the National Registry of Certified Microbiologists ("NRCM") and the satisfaction of the ABSA's experience requirements. See, http://www.absa.org/biocert.html. The American Society for Microbiology ("ASM") certifications are the responsibility of the American College of Microbiology and include certification by the NRCM of microbiologists at various levels, certification by the American Board of Medical Laboratory Immunology of doctoral-level immunologists seeking to direct laboratories, and certification by the American Board of Medical Microbiology of doctoral-level microbiologists seeking to direct laboratories. See, http://www.asm.org/index.php/certification.

[22] For example, Condition 3 provides in part: "The effectiveness of all thermal inactivation systems shall be demonstrated through initial testing in accordance with generally accepted industry standards and the destruction standard in Condition 23. . . . Chemical inactivation of laboratory waste and research and development material shall be conducted in accordance with generally acceptable industry practices for the inactivation of infectious waste. These practices shall be consistent with guidelines developed by the Association of Analytical Communities (AOAC), Centers for Disease Control (CDC), the National Institutes of Health (NIH) and/or other scientifically accepted protocols."

The stated objectives of the proposed amendments to Chapter 284 include providing permits-by-rule for certain processors of regulated medical waste using autoclave, incineration, steam or superheated water and chemical treatment techniques and simplifying testing requirements for autoclaves. Preamble at 4858. By incompletely addressing the concerns of manufacturers of vaccines and other biologics, the proposed amendments do not fully meet these objectives. For captive processing facilities disinfecting waste produced at the biologics production site, the expertise, infrastructure, technology and protocols of biologics manufacturers support adopting disinfection methods and monitoring, validation and waste handling and disposal regulatory provisions specific to their unique activities.

RECOMMENDATION:

Based on the foregoing, Merck and Sanofi Pasteur recommend that the following regulatory amendments to §§ 284.321[23] and 284.322 be adopted:

284.321(p): 1. Applicability. This subsection applies to vaccine or other biologic manufacturers classified under the North American Industrial Classification System (NAICS) as Code 325414 – Biological Protocol (except Diagnostic) Manufacturing, and who (i) utilize on-site processing facilities at which at least 50% of the waste processed is generated on-site, (ii) operate in accordance with FDA good manufacturing practices (GMP) or good laboratory practices (GLP), (iii) employ a production process where the infectious biological agents are known and well characterized, inactivation criteria are determined and bioburden is measured and controlled including screening for objectionable organisms, and (iv) specify and approve the decontamination process, method and monitoring and validation procedures for each specific infectious agent in its waste by (1) establishing and utilizing an Institutional Biosafety Committee constituted in accordance with CDC/NIH guidelines or composed in whole or in part of a panel of experts a member of which is a biosafety officer certified by the American Biological Safety Association or the American Society for Microbiology or equivalent and/or (2) retaining a contractor certified by the American Biological Safety Association or the American Society for Microbiology who accepts responsibility for the process, method and procedures that the contractor specified and approves ("independent Certified Biosafety Professional").

2. Alternative Disinfection Requirements: Vaccine or other biologic manufacturers satisfying the applicability conditions in subsection (p)(1) may employ the following regulated medical waste disinfection procedures in lieu of the requirements in the other subsections of this §284.321 to process waste containing an infectious agent classified as Biosafety Level 2 or below.

(1) Disinfection shall be conducted by inactivating all waste materials in accordance with the practices, methods and minimum parameters for biological kill established by the facility's Institutional Biosafety Committee and/or independent Certified Biosafety Professional consistent with CDC and NIH guidelines and/or scientifically accepted protocols.

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[23] Amended § 284.2(a) would provide a permit-by-rule to an autoclave facility. The permit-by-rule incorporates the operating requirements of § 284.321. Therefore, changes to § 284.321 apply to facilities covered by the permit-by-rule.

(2) Efficacy of the inactivation operations shall be demonstrated through review of decontamination cycle data by trained technicians or other testing methods or studies specified by the facility's Institutional Biosafety Committee and/or independent Certified Biosafety Professional as appropriate for the specific biological agent present in the waste. The procedures for demonstrating the efficacy of the inactivation operations shall be set forth in standard operating procedures and/or other written procedures maintained at the facility.

(3) Preventative maintenance and calibration programs for decontamination equipment consistent with generally accepted industry standards as specified by the Institutional Biosafety Committee and/or independent Certified Biosafety Professional shall be established and routinely implemented.

284.321(q): With the exception of used sharps, which remain subject to the additional requirements that this Chapter imposes on used sharps, regulated medical waste that is generated by manufacturers of vaccines and other biologics who satisfy the applicability criteria of subsection 284.321(p)(1) and decontaminated in accordance with the procedures specified in subsection 284.321(p)(2), may be managed, stored, transported and disposed of as ordinary municipal or residual waste and shall not be subject to any of the additional restrictions or requirements pertaining to special handling waste or regulated medical waste.

284.322(8): In lieu of the temperature, residence time and other requirements of this section 284.322, manufacturers of vaccines or other biologics who satisfy the applicability criterion of subsection 264.321(p)(1) may establish and validate autoclave operating parameters and residence time based upon the requirements determined by the manufacturer's Institutional Biosafety Committee and/or independent Certified Biosafety Professional as necessary to achieve the required disinfection under §284.321(p)(2) for the specific infectious agent and/or biologic present in the waste.

VII. Certain of the Proposed Amendments of General Applicability Will Facilitate Compliance by Operators of Biologics Facilities and Should Be Adopted.

Merck and Sanofi Pasteur support the following proposed amendments to the ICW regulations because they will assist in implementing compliance programs that also meet business needs:

At present, 25 Pa. Code § 284.321(b) requires the operator of a facility that incinerates or thermally processes infectious waste to submit to the Department a microbiological analysis of a composite sample of the processing or ash residue on a quarterly basis. The proposed amendment to this subsection changes the frequency of the submission to an annual basis to be consistent with the schedule for submission of chemical analyses contained in subsection (c). Merck and Sanofi Pasteur believe that coordination of the microbiological and chemical analyses submissions is a proper and helpful administrative change.

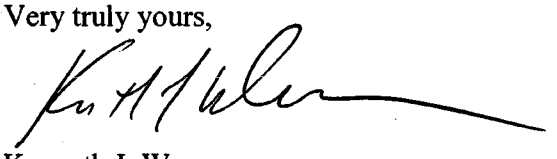
At present, several subsections of Part 284 require the management of ICW based on the date on which the waste was generated or first placed in the container. *See, e.g.*, 25 Pa. Code §§ 284.413(a) and 284.416(b)(2). The proposed amendments would manage regulated medical waste based upon when the container was full or sealed, whichever occurs earlier. *See* proposed §284.415. Merck and Sanofi Pasteur support this change because it will facilitate the determination of when permissible storage times have elapsed and will allow for more complete use of containers, thereby reducing the number of containers that must be transported and processed or disposed. This change promotes laudable goals of adding clarity to the regulations and assisting regulated biologics manufacturers ensure the safety and cost effectiveness of their waste management activities.

At present, the ICW regulations require use of a paper manifest tracking system to track shipments of ICW. *See, e.g.*, 25 Pa. Code §§ 284.702 (manifests for transfer facilities) and 284.711 (preparation of manifests by generator). The proposed changes to these regulations allow for the use of shipping papers or logs, including electronic tracking systems. Merck and Sanofi Pasteur believe that advances in technology have made electronic systems reliable and less cumbersome to use than existing paper manifests. Accordingly, we support this change.

At present, records required by subchapter H of part 284 (manifesting) must be retained for at least five years. 25 Pa. Code § 284.703. The proposed amendments to this section would clarify § 284.703 by eliminating subsection (b), would reduce the record retention time to two years and would clarify the date on which the retention period commenced. Merck and Sanofi Pasteur agree that the additional clarity will be helpful in the administration of the ICW program and that the two-year record retention period is reasonable.

Merck and Sanofi Pasteur thank the Board and the Department for their consideration of these Comments. Should you have any questions, please feel free to contact me.

Very truly yours,



Kenneth J. Warren

KJW/sl