AMERICAN SOCIETY FOR MICROBIOLOGY

Public and Scientific Affairs Board

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Centers for Disease Control and Prevention
Division of Select Agents and Toxins
1600 Clifton Road
MS A-46
Atlanta, GA 30333

Subject: Comments on the changes to the HHS list of select agents and toxins

The American Society for Microbiology (ASM) is submitting the following comments on the July 21, 2010, Department of Health and Human Services (DHHS) Advance Notice of Proposed Rulemaking (ANPR) request for comments on the biennial review of the HHS list of select agents and toxins, including whether any agent or toxin should be removed from the list, whether the list should be tiered based on the relative bioterrorism risk of the agent or toxin, and corresponding changes to security requirements. The ASM is the largest single life science society with approximately 40,000 members dedicated to the study and advancement of scientific knowledge of microbiology for the public benefit.

The study of pathogenic microorganisms, including select agents, is essential for the biosecurity of the United States. Research is needed to find protective vaccines and therapeutic drugs and diagnostic activities are critical for protecting individual and public health. The legislation that led to the select agent regulations recognizes that some select agents may pose a greater threat to the public health and safety than others and specifically states that security requirements should be "commensurate with the risk of the agent and toxin, including the risk of use in terrorism."

Stratification of the HHS Select Agent List and Biosecurity Requirements

The ASM believes that biosecurity requirements, including personnel clearance requirements, could be stratified to be commensurate with risk. The ASM recommends that the select agent regulations be tiered so that biosecurity requirements are commensurate with the risk that a particular agent could be misused to do significant harm. Changing to a tiered system would allow the focus to be on agents that pose the greatest danger. It could reduce the regulatory burden and thus permit critical research

activities that will provide real protection to proceed. Additionally, tiering and reducing the number of agents requiring the highest levels of biosecurity could increase the likelihood for international harmonization that would greatly increase biosecurity.

The ASM believes that the current oversight mechanisms for select agents, including biosecurity and personnel clearance requirements, are best suited for those agents that are included in Tier 2 in the ASM proposal. Higher levels of biosecurity and personnel clearance would be appropriate for facilities that handle the agents listed in Tier 1 in the ASM proposal. In contrast, reduced levels of biosecurity and personnel responsibility should be strongly considered for the agents designated as Tier 3 to the degree that such reductions are consistent with existing federal legislation.

The ASM believes that those who work with select agents are responsible for the safe and secure handling of pathogens under their control. However, the requirement to account for individual vials of pathogens is inappropriate for a replicating agent and is burdensome and costly for laboratories. The single exception is for Tier 1 agents where limited access to variola major and minor is already in place and consistent with WHO guidance. For Tier 2 and 3 agents, we recommend elimination of the requirement for counting individual vials of agents.

We also recommend that the current Security Risk Assessment screening process should include an appeal process to consider the circumstances surrounding otherwise disqualifying factors as recommended by the NAS report Responsible Research with Biological Select Agents and Toxins.

Tiering of the HHS Select Agent List

The ASM recommends retaining an agent based list for tiering. Biosecurity requirements should be aligned with the public health risk categories established by the Centers for Disease Control and Prevention (CDC) and with special international agreements. The CDC Category A and B agent lists would capture all biological agents for which material threat assessments have been made and all agents reported by USAMRIID to have been weaponized except for T2 Toxin.

Consideration should be given to adding a highest category for major threat agents that have been extinguished from nature and which require special consideration due to international agreement. This highest tier should be given to agents that pose major human health risk, exist only in laboratories where the US has a monopoly or near monopoly and for agents controlled according to WHO agreement. The agents on this top tier would include:

- Variola major virus (Smallpox virus)
- Variola minor virus (Alastrim)

- Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed1918 Influenza virus)

The second tier should be aligned with the remaining CDC Category A agents , which include organisms that pose a risk to national security because they can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness. Agents in this second tier would include:

- *Bacillus anthracis*
- Botulinum neurotoxins
- Botulinum neurotoxin producing species of *Clostridium*
- Crimean-Congo haemorrhagic fever virus
- Ebola virus
- *Francisella tularensis*
- Lassa fever virus
- Marburg virus
- *Yersinia pestis*
- South American Haemorrhagic Fever viruses: Guanarito; Junin; Machupo; Sabia

A third tier, which should have lower biosecurity requirements, would include agents that are moderately easy to disseminate and result in moderate morbidity rates and lower mortality rates. Agents that would be included as Category 3 agents are:

- *Coxiella burnetii*
- Eastern Equine Encephalitis virus
- *Rickettsia prowazekii*
- Staphylococcal enterotoxins
- *Brucella abortus*
- *Brucella melitensis*
- *Brucella suis*
- *Burkholderia mallei (formerly Pseudomonas mallei)*
- *Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)*
- Hendra virus
- Nipah virus
- Rift Valley Fever Virus
- Tick-borne encephalitis complex (flavi) viruses
  Central European Tick-borne encephalitis; Far Eastern Tick-borne encephalitis;
  Kyasanur Forest disease;
  Omsk Hemorrhagic Fever;
  Russian Spring and Summer encephalitis
- Venezuelan Equine Encephalitis virus

- Ricin
- Abrin

The ASM also recommends that several agents be eliminated from the select agent list due to their wide distribution in nature, lack of ease of production, and/or limited pathogenicity. Agents that ASM recommends eliminating from the select agent list include:

- *Coccidioides posadasii/Coccidioides immitis*
- *Rickettsia rickettsii*
- Monkeypox virus
- Cercopithecine herpesvirus 1 (Herpes B virus)
- Flexal from the South American Haemorrhagic Fever Viruses
- Saxitoxin
- Shiga-like ribosome inactivating proteins
- Shigatoxin
- T-2 toxin
- Tetrodotoxin
- Conotoxins
- Diacetoxyscirpenol
- *Clostridium perfringens epsilon toxin*

Justifications for eliminating *Coccidioides posadasii/Coccidioides immitis, Rickettsia rickettsii,* Monkeypox virus, Shiga toxin, Flexal and Herpes B virus:

- *Rickettsia rickettsii*

The assignment of select agent status to the agent *Rickettsia rickettsii* seems to be based on its relatedness to other potential biological weapon agents (*Coxiella burnetti*) and pathogens of military significance such as *Rickettsia prowazekii* than to its potential as a biological weapon. Although the primary disease associated with *R. rickettsii*, Rocky Mountain Spotted Fever, is serious and potentially life-threatening, the biological properties of this pathogen make it a rather unfit agent for deliberate transmission. The bacteria are fastidious obligate intracellular pathogens, thus propagation requires growth in cultured host cells. The fragility of the organism does not allow for purification of infective particles of high titer from such cultures as is achievable for many viruses. Natural infection occurs by parenteral inoculation through a tick vector, so mass exposure by aerosolization or contamination of food sources is unlikely to result in disease. Genetic manipulations of this bacterium are extremely difficult due to its obligate intracellular lifestyle so the potential to use this agent as a platform to construct a genetically engineered new pathogen would be extremely difficult. Finally, disease associated with *Rickettsia rickettsii* is not uncommon, hence the symptoms are recognizable and diagnostics and treatment for Rocky Mountain Spotted Fever are readily available. The agent is a biosafety risk to those working with it in the lab because

of its virulence, but that does not equate to the risk or likelihood that it could successfully be used as a bioweapon.

- Monkeypox virus

Effective vaccine is available and promising antivirals are in advanced stages of development. Between 1981 and 1986, the case-fatality rate of human monkeypox in the Democratic Republic of the Congo (Congo Basin strain) was approximately 10% for all ages. If the analysis was restricted to subjects aged 6 years of age or greater, the case-fatality rate was only 2.4%. More recent investigations suggest a lower case fatality rate (2-3%); this may be affected by the disease demographics. There have been no documented case-fatalities associated with West African strains in Africa. The 47 probable or confirmed cases of human monkeypox associated with the 2003 importation of a West African strain from Ghana into the Midwest of the USA were associated with no case-fatalities. Only 2 cases had severe morbidity, one with oropharyngeal edema and airway compromise, the other a case of encephalitis. In Africa the Congo Basin strains of MPXV were associated with a secondary attack rate of ~9%, and chains of transmission that rarely exceed 4 generations. No examples of human-to-human transmission of West African strains have been documented in Africa. In the 2003 USA out break of human monkeypox caused by a West African strain, there was no observed chain of human-to-human transmission. MPXV infection leads to relatively low case fatality rates in humans; clinically severe human West African MPXV disease is rare and this virus clade has not been associated with human mortality. An effective licensed vaccine is available that protects against MPXV infection; The licensed antiviral drug, cidofovir, is available and likely to be beneficial in off-license treatment of human MPXV infections, and two orally available antivirals, ST-246 and CMX001, will likely be licensed in the future; MPXV is inefficiently transmitted from person-to-person; West African MPXV has not been characterized to transmit between humans.

- *Coccidioides posadasii/Coccidioides immitis*

There are at present only two species in the genus *Coccidioides*. *Coccidioides immitis* and *Coccidioides posadasii* are clinically and pathologically virtually identical as far as data suggests at this time. Using phenotypic characteristics and/or the genetic probes, it is not possible to differentiate between the two species at the routine clinical laboratory level. Specialized molecular means of differentiation is required.

Numerous articles published on the subject of bioterror agents do not include *Coccidioides* species as possible agents. The CDC derived their critical biological agents list by using the Australian Group List for Biological Agents for Export Control, military information, the Biological Weapons Convention, and the WHO biological weapons list for review. Indeed, the CDC's listing of potential bioterrorism agents (complied by experts from DHHS, civilian and military experts, and law enforcement officials), does not include this organism as a potential bioterror agent.

Present regulations pose major burden in time and restrictions in ability to provide data in clinical laboratories working with the organism (especially in the endemic areas). Some laboratories in the SW United States recovers approximately 300 isolates a year. Increases time for administrative functions connected with reports to the CDC at a time that laboratorians are overworked and difficult to find in the work force.

Susceptibility surveillance, epidemiologic studies, as well as special studies (often requested by clinicians days or weeks after isolation of an organism) difficult if not impossible to accommodate under the present regulations. Public Health and individual patient course impacted directly.

The following discussion regarding *Coccidioides* species includes factors relating to each of the current criteria for use when deciding if an organism is of such a threat that it belongs on the official select agent list.

1. Degree of pathogenicity: The common syndrome is a relatively mild, self-limited respiratory illness. Although coccidioidomycosis is the 4th most common infectious disease reported to the Arizona Department of Health Services (Comment: the ADHS counts any serology, even a single EIA IgM by itself, as a positive Coccy case, thereby probably overcalling the overall number of cases) it is not as pathogenic in humans as are other species such as *Mycobacterium tuberculosis* (yet MTB is not presently regulated). Of the estimated 100,000-150,000 new infections annually in the United States, approximately 60% are asymptomatic. Only 40% of patients who acquire infection naturally have any recognizable symptoms which may include cough, fever, arthalgias, myalgias, and fatigue. In most patients, symptoms resolve or significantly improve within 2-3 weeks. Less than 10% show more symptomology, and less than 1% show serious disease with dissemination. Inocula need to be fairly high for the organism to be able to overpower the host in non-immunocompromised patients.

2. Communicability: Although coccidioidomycosis if the 4th most common infectious disease reported to the Arizona Department of Health Services (Note: same reporting issue as above), it is not contagious and there is no direct person to person transmission (1, 5). Again, this is unlike MTB which can be transmitted from person to person.

3. Ease of dissemination: Although the arthroconidia are airborne fairly easily and transmitted via the respiratory tract, they require sustained, fairly strong wind activity (dust storms, etc) to remain airborne and to become disseminated in an enclosed space causing human infections. Unlike MTB, which can remain in the air for greater protracted time periods (greater than 20 mins), arthroconidia are quite dense and cannot remain in the air without the sustained air activity. Most naturally-acquired infections occur on windy, dusty days.

4. Route of exposure: Coccidioidomycosis is an infection resulting from inhalation of airborne spores from the soil and it is almost exclusively transmitted via the respiratory

tract. By comparison, infection via direct inoculation is extremely uncommon, and via oral ingestion almost unheard of. Sustained air flow is necessary to maintain arthroconidia in air. Respiratory route of exposure is more difficult to maintain as air becomes more humid (as in parts of the country outside of the SW deserts) and propulsion of arthroconidia for longer distances through wet air becomes more difficult.

5. Environmental stability: The arthroconidium has a very heavy wall and can withstand desiccation and other adverse conditions very well. But their survival is apparent in specialized conditions in which they are likely protected from the natural environment. *Coccidioides spp*. cannot compete against other organisms in the environment and quickly die out when placed in an environment with competing organisms. Thus, their presence in the desert soils is restricted to specific discrete locations where other competitors are quickly killed off by the sun, etc. Areas in which they are found seem characterized by the presence of fine, silty sand. They are not found in tilled soils (such as farm land) and much less of a problem in urbanized areas, even in endemic areas. They are unlikely to remain as environmental problems outside of their areas of endemicity. Options for environmental control of coccidioidomycosis are limited.

This is borne out by the many climatic variables that are significantly associated with increased incidence of disease, including prolonged drought, wind velocity, mean temperature, dust and rain. There is a high correlation between incidence of disease and 1) cumulative rains during the preceding 7 months, 2) the average temperature during the preceding 3 months, 3) dust during the preceding month, and 4) the amount of rain during the preceding 2 months in proportion to the preceding 7 months. Epidemics have been associated with dust storms, and earthquakes.

6. Ease of production: It should be fairly easy to acquire this organism from desert soils and to propagate *Coccidioides spp*. One would not need clinical laboratories from which to acquire isolates as they presumably could isolate them from the desert themselves. According to a recent review, terrorists would likely encounter significant difficulties in attempting to employ the organisms as effective weapons.

7. Ability to manipulate genetically: There is no indication that it is easier to genetically alter *Coccidioides spp.* into super-bugs than it is other bacteria and/or viruses and fungi (as to their increased virulence, pathogenicity or longevity). *Coccidioides spp.* do not seem to have the innate variety of virulence factors that many other bacteria have, so it is probably harder to make these into super-bugs.

8. Long term effects: Long term effects are seen in a small group of patients who acquire the disease (less than 5%). These effects are usually seen in patients who have not received early intervention with antifungal agents. Progression of the disease to these conditions is relatively slow and if diagnosed early, usually is preventable. This would not be a major problem during a possible biological bioterrorism event, as early epidemiologic data would allow antifungal intervention.

9. Acute morbidity: Again, less than 40% of patients show symptoms and less than 1% have severe problems with possible mortality. It would require much higher concentrations of arthroconidia to cause consistent, increased morbidity and especially mortality. This concentration would be difficult to deliver to a large group of victims (even in an enclosed environment) as it would require a consistent, large amount of air pressure or wind.

Dissemination may occur rarely, as stated earlier, after the primary pulmonary infection, or the infection may be chronic and relapsing, like tuberculosis, and may be contained, rather than destroyed by the immune response.

10. Acute mortality: As a whole, mortality is low even without antifungal intervention. Early antifungal therapy would lower mortality even further.

11. Availability of therapy: Many active antifungal agents are now readily available against coccidioidomycosis. Fluconazole, itraconazole, voriconazole, posaconazole, amphotericin, and the newer echinocandins are all now available. Early intervention (either prophylactically or therapeutically) should greatly mitigate an unlikely biological bioterrorism event with *Coccidioides spp*. Indeed, for most patients with mild respiratory illness (which is the majority of patients with symptomology) many authorities believe that antifungal therapy is not necessary.

12. State of immunity: Infection usually produces life-long immunity to reinfection (3, 7). Most patients who have normal immune function overcome infection with this organism with either no or minor symptoms and on the whole become immune to further challenge.

13. Vulnerable populations: The chance of acquisition of coccidioidomycosis is equal amongst patients. Immunocompromised patients, those of certain ethnic backgrounds, and those in their third trimester of pregnancy have significantly higher rates of dissemination. However, these populations should make up a small percent of total number of persons exposed in an event and early antifungal intervention would allow patients to do well and perhaps not disseminate.

14. Burden or impact on Health Care System: The impact should not be any different than with other naturally occurring and fairly common outbreaks we are experiencing at this time. These recent outbreaks have included *E. coli* (hemorrhagic), *Salmonella*, *Shigella*, and *Cryptosporidium*, etc. Although these have financial and health impact, they do not carry the fear factors seen with outbreaks of anthrax, smallpox, plague or other rarely seen pathogens. An outbreak of MTB would probably cause a greater public concern than an outbreak with these other diseases, including coccidioidomycosis.

Based upon the above characteristics Coccidioides *spp*. do not provide convincing properties of an effective agent of bioterrorism. They are endemic in the SW U.S., but do not cause large epidemics even with high prevalence in the air during wind storms. Increase of cases may be directly related to the rapid growth in the SW and the migration of a large virgin population to the area together with increase desert soil disruption for housing. They are not as pathogenic or virulent as many other bacterial, viral and fungal species. They are a greater burden to propagate, manipulate and deliver in an event, without providing an equal threat to public health. The are easily treatable, especially early in disease. The biological agents used for warfare must be easily produced and dispersed, have a delayed onset, cause high rate of morbidity and mortality, and present unique challenges in diagnosis, detection and treatment. These are not characteristics of *Coccidioides* species. The difficulty to use *Coccidioides* species as a bioweapon, and hence the need for strict regulation under the select agent rule, is exemplified by its non-communicability, lack of history of use or development as successful biological weapons, and a relatively low incidence of symptomatic disease following natural infection. The public health consequences, and hence the need for strict regulation under the select agent rule, of a deliberate release of *Coccidioides* spores among a susceptible civilian population are uncertain and most probably limited.

- Shiga toxin and Shiga type ribosome inactivating toxins

The ASM recommends that Shiga toxin and the Shiga type ribosome inactivating toxins and particularly the DNA that encodes these toxins be removed from the select agent list. The reasoning that supports this position is based on our knowledge gained over several years of research with these toxins and the HHS Secretary's criteria for inclusion of toxins and agents on the select agent list. Our comments address the Shiga and Shiga type toxins in the first part of the discussion, and the DNA that encodes such toxins in the second part.

Shiga toxin and Shiga-type toxins.

1a. Toxicity and route of exposure: Although microgram per microgram, the Shiga toxins (Stx), (particularly Stx type 2) are nearly as toxic as botulinum toxin when given parenterally to mice (which is the likely reason for their initial inclusion on the Select Agent list), the route by which an individual becomes intoxicated by Stx is more restricted, requiring that a person become infected with a Shiga toxin-producing bacterium. Little data is available that indicates Stx is toxic when administered orally. However, one recent mouse study of oral Stx2 intoxication showed that when toxin is given intragastrically, the dose of Stx2 lethal to mice is 10,000-fold more than the lethal dose when toxin is administered parenterally. One possible conclusion of this work is that the gastric pH inactivates a considerable portion of the ingested toxin. Therefore, to obtain a lethal oral dose for a human proportional to that observed in the mouse study (2 mg/kg) would require efficient purification of toxin from 6,000 to 10,000 L of culture of toxin-expressing bacteria, a process that is technically demanding and highly inefficient.

In contrast, the normal route by which humans are exposed to Stx is through ingestion of Shiga-toxin producing strains of *E. coli* (STEC) that colonize the gastrointestinal mucosa and elaborate toxin that is absorbed systemically via an unknown mechanism. Thus, it appears that interaction of toxin-expressing bacteria with the gut is necessary for systemic intoxication with Stx to occur. We expect that aerosolized toxin may be harmful to humans, but logistically it is very hard to produce Stx in large quantities or to administer on a large scale via the aerosol route. Parenteral administration of Stxs is likely a lethal route (as is well documented in animals); however, the above-mentioned problems of purification of large quantities of toxin, as well as the fact it is difficult to access to the public via the intravenous or intramuscular route, make administration by injection unlikely.

2a. The degree of contagiousness: The criterion does not apply to toxins.

3a. Available pharmacotherapies and immunizations to protect against Stx: Strategies for treatment of Stx intoxication have been developed as interventions to natural exposure via infection with STEC, although none is commercially available or FDA approved at this time. The most effective treatment is likely to be humanized monoclonal antibodies specific for the neutralization of the two major groups of Stx, Stx type 1 and Stx type 2. Such therapies are in Phase II clinical trials. Strategies for immunization against exposure to Stx have also been described in the scientific literature. A vaccine that protects against Stx1 has completed phase 2 trials and not FDA approved.

4a. Potential for use as a bioweapon: The use of Shiga toxin as a bioweapon is severely constrained by the very low yield of toxin from cultures, even when the toxin genes are encoded on recombinant DNA that is expressed under optimal laboratory conditions (in expression vectors and expression host *E. coli* strains). In addition to low yield in culture, methods of purification of the toxin from culture supernatant are very laborious and produce very small amounts of toxin. In particular, the complex non-covalently linked AB5 structure of Stx precludes the use of molecular tags such as the addition of repeat histidine residues to facilitate purification of the toxin by Histidine affinity to nickel, because such tags reduce the activity of the toxin (presumably by inhibiting toxin assembly).

5a. Needs of children and other vulnerable populations: Children (and the elderly) have a higher risk of poor outcomes following **infection** with STEC. The basis of this increased susceptibility is likely to be multi-faceted, but children are thought to have more toxin receptors on endothelial tissue that do adults. Their increased risk during infection is also likely to be related to factors that influence colonization with STEC in addition to their increased susceptibility to toxin elaborated by such bacteria. It is unknown if direct Stx administration to children via any route is more profound that the reaction anticipated for adults.

Recombinant DNA that encodes Shiga or Shiga type toxins:

1b. Effect on human health upon exposure: The DNA that encodes Stx is not inherently harmful to humans, nor is it infectious. Laboratory strains that harbor recombinant DNA on plasmids require antibiotic selection for the plasmids to be retained in those strains and because such laboratory *E. coli* strains lack the adherence and other virulence properties found in wild-type STEC, they are thought to be attenuated compared to the wild-type STEC. Hence, the DNA and bacteria harboring recombinant DNA are considered less virulent than naturally occurring strains such as the (non-Select Agent) *E. coli* O157H7.

2b. Contagiousness: Recombinant DNA that encodes Stx is not infectious. Lab strains of *E. coli* that harbor recombinant DNA that encodes Stx are considered to be less fit as pathogens than the wild-type O157H7 or other STEC parent strains.

3b. Availability of therapeutics and vaccines (same as #3a)

4b. Suitability or potential for recombinant DNA encoding the Shiga type toxins to be used as a biological weapon: Although rDNA could theoretically be used to mass produce toxins encoded therein, our vast experience in trying to produce toxin from rDNA for the purpose of research has shown that even when recombinant methods are optimized for expression of such proteins, the yield is very poor. Furthermore, purification or concentration of the resultant toxin is highly inefficient and requires antibody affinity, and FPLC to achieve even modest yields. For example, 6-10 L of culture may yield only 100 micrograms of toxin (1000 times less than the select agent limit) and requires several weeks to purify. Our view is that this renders Stx recombinant DNA a very poor source for generation of toxins that would be useful for even limited bioweaponization and useless if intended to elicit mass casualties. Furthermore, such toxin would likely only be useful if administered via parenteral routes, a situation that is not likely applicable to mass administration. Finally, the ability to synthesize such DNA requires very modest skills and equipment (PCR amplification), and the host organisms to provide a template for DNA amplification of toxin genes is relatively ubiquitous in that the STEC strains are found in nature, in our food supply (ground meat in the grocery store) and isolated from patients routinely in clinical microbiology labs. Therefore, rDNA is neither an esoteric commodity nor a very useful one, in comparison to other toxins and agents on the Select Agent list.

- Herpes B virus

The virus is widely available in nature and not efficiently transmitted by aerosol route. There is only one case of person to person transmission, and this appears to have been a unique situation unlikely to be frequently replicated. Given the high prevalence of infection in NHP and the relatively few human infections that have been recorded, it

suggests that the virus is not easily transmitted to humans. In some respects, this is similar to rabies, albeit without an effective vaccine.

- Flexal

This is a legacy agent based on some historical comments about a single infection (lab acquired) that resulted in a febrile illness with some evidence of hemorrhage. We are unaware of any significant outbreaks or any deaths attributed to infection with this virus.

We appreciate the opportunity to comment on the ANPR and look forward to reviewing the proposed changes to the Select Agent regulations.

Sincerely,

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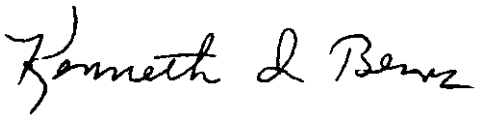

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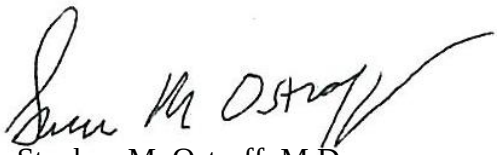

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