National Organic Standards Board
Crops Subcommittee
Petitioned Material Proposal
Streptomycin

August 6, 2013
***Reviewed and revised February 18, 2014**

Discussion Summary:

The NOSB has been petitioned to remove the existing expiration date of October 21, 2014 for Streptomycin and replace it with a new one of Oct 21, 2017, for both apples and pears. The petitioner states that this would allow adequate time for the transition from strep over to non-antibiotic, biological alternatives for fire blight control.

There are two different positions on this subject: those that support the petition request for an extension and those that oppose an extension.

Both sides agree that it is time for a phase out for the allowed use of strep. The supporters believe that three additional years until October 2017 is reasonable, and opponents believe that yet another extension offers no assurance of phase out.

Proponents of an extension feel that:

~Because of the investment involved to establish an orchard (as well as the businesses established to handle this produce) in both time, money, and the need for completion of existing research of materials, that a slowdown (or extension) of the expiration date is needed, especially for pear growers.

~This slow down would benefit growers, processors, producers, handlers, and consumers alike.

~Alternative materials are still not readily showing consistent control and one material's registration (Previsto copper) has been delayed by EPA. Thus, the farmers still need some additional time in order to prepare for the transition to a non-antibiotic fire blight control period in time.

•Opponents feel that:

~Fire blight resistance to streptomycin is widespread in the U.S.

~Raise the question of essentiality, based on the significant percentage of growers selling to markets that do not allow antibiotic treatments.

~Organic integrity and sales are threatened because of consumer expectation that antibiotics are not used in organic production.

•Both sides agree that the "core" issue here is whether or not there is a risk of enhancing antibiotic resistance in human pathogens. There is science that supports both sides of this argument and the level of concerns that are raised by this particular use pattern. Supporters cite issues of use patterns and limits of residues as indicative of no evidence of harm. Opponents cite resistant human pathogens in strep treated orchards and horizontal gene transfer identified as leading to antibiotic resistance.

•While there has been a direct linkage shown to exist between infection and colonization of humans by antibiotic resistant bacteria in animals (Larsen et al 2010), supporters cite no direct linkage has been demonstrated between antibiotic resistant bacteria in humans and antibiotic sprays applied to plants (Stockwell and Duffy, 2012), such as the current use of strep in apples and pears for fire blight control. Lab results vary in their conclusions. Opponents cite evidence that bacteria, including *Erwinia amylovora* and human pathogens, share a common genetic basis for resistance, transmitted by plasmids, to streptomycin in particular. (McGhee et al, 2010; Sundin, 2000; Sundin and Bender, 1996; Pezzella et al, 2004; Scherer et al, 2013; Foster et al, 2004.)

•Proponents state: there is no evidence that applications of antibiotics to orchards during bloom contributes to antibiotic resistance in human pathogens. The amount and timing of the use of strep in an orchard environment does not contribute to any human health concerns, especially in light of streptomycin being ineffective in humans when ingested orally.

•Opponents state: there is evidence that an application of strep leads to an increase in resistance to streptomycin in orchard bacteria, that human pathogens and fire blight bacteria share the same gene pool of genes resistant to streptomycin (i.e. that the same genes responsible for resistance in Erwinia amylovora are also responsible for resistance in human pathogens), that human pathogens do not need to be present in the orchard to obtain resistance genes acquired by and augmented in orchard bacteria, that strep residues are sometimes present in treated fruit, and that strep is still a critically important antimicrobial for use against human pathogens.

•The primary point of discussion here is whether to grant an extension or not to the current expiration date for streptomycin in October 2014. The points proponents say should be considered are: What impact does an extension/or non-extension have on the stakeholders that either use this material or have built their businesses around expanded crop availability; How will a decision impact the supply chain, How will a decision impact the consumer (all consumers, not just a select group(s)), What are the risks/if any for granting an extension or not, and would granting a short extension for allowed use knowing what the use patterns are pose any significant increases in human health concerns from resistance than currently exist today?

•The points opponents say should be considered are: What impact does yet another extension, which was first called for by the NOSB in 1995, have on the integrity of the organic label? What are the public health hazards of using antibiotics for nontherapeutic uses and why are infectious disease doctors concerned? What is the threat of low-level environmental exposure to antibiotics? What are the alternative strategies that are used to manage or prevent fire blight?

•Remember, according to proponents, this is not a new material, but one that has been on the National List of Approved Materials for a number of years as being allowed for use by organic growers to use on their organically grown and certified crops. Opponents point to long-standing NOSB attempts to phase out the use of antibiotics in organic apple and pear production, with votes by previous boards to phase-out, only to have subsequent boards issue extensions.

•One other point of discussion, proponents state that this would be a way to ensure a full expiration of strep from the National List, if an extension for use were to happen. They ask, how could we ensure all stakeholders that there would be an absolute point when this usage would truly expire? Opponents, who would like the 2014 antibiotic expiration date to take effect, believe that the debate on antibiotics and votes to phase them out by previous boards have resulted in only extended deadlines for too long, and organic should not in any way contribute to the worldwide crisis in antibiotic resistance, while ultimately threatening consumer confidence in the organic label.

New text:

Oral and written public comments (Docket AMS-NOP-13-0049) from pear growers noted that especially in the 2013 season, Blossom Protect did not work well in the Pacific Northwest and California. (The manufacturer of Blossom Protect does not agree with this statement and voiced their disagreement during the written public comment period prior to the canceled fall 2013 NOSB meeting.) It was an unusually warm spring. The copper material that is very promising has been delayed in registration until at least 2014 nationwide and 2015 in California.

Summary of Proposed Action:

The Crops Subcommittee proposes to:
Remove the existing expiration date of October 21, 2014 for streptomycin and replace it with a new expiration date of October 21, 2017. This would be for use in both apples and pears for control of fire blight.

The Crops Subcommittee puts forward this resolution:

Resolution: The National Organic Standards Board is committed to the phase out of this material. Between now and the expiration date the Board urges growers and certifiers to include in organic systems plans an annual increase in the extent and/or number of alternative practices and materials that are trialed for controlling fire blight. In addition, the board strongly advocates to USDA a high priority for increased support for research into these alternative practices and materials.

Introduction

A Petition to the National Organic Standards Board (NOSB) was received for the Removal of the Expiration Date (October 21, 2014) for streptomycin and the establishment of October 21, 2017 as its sunset date, in order to allow for adequate time for the transition to proven effective non-antibiotic, i.e. biological alternatives for fire blight control in apples and pears.

Because this subject is complex and there are two different positions to be represented, this recommendation is organized to present two separate positions - those for and those against an extension. These are designed to supplement the points raised in the checklist. Most of the same background presented in the spring 2013 Recommendation for Oxytetracycline is relevant to Streptomycin, except for the 2007 and 2008 actions.

The subcommittee acknowledges the concerns of consumers and previous NOSB members who feel that it is time to phase this material out from organic agriculture. The two positions represented in the discussion section of this document differ on the timing of the phase-out. Additional concerns are being put forward in a separate resolution on the subject.

Points of Agreement and Disagreement

This section focusses on how the material is used in the context of both plant and human health. Because much of the general information was covered in the proposal for Oxytetracycline, this review focusses on the differences and similarities between the two materials. Specific portions address Checklist categories as noted.

1. Fire blight control
Proponents of both positions agree that orchard establishment requires a large investment of time and money, that apples and pears are grown in a variety of locations that require different management plans, and that more research is needed into systems for preventing fire blight damage.

Proponents of extending the expiration date of streptomycin say:

- Because of the very large investment of time and money that establishing an orchard entails, the variety of locations that apples and pears are grown, and the very rudimentary state of research on alternatives to this material in that variety of locations, we are supporting slowing down the removal of streptomycin from the National List.

- Since the organic pear industry is more at risk to fire blight than apples there is concern that pear research and control measures are lagging behind and that an expanded time frame will be needed. Streptomycin is still fairly widely used in pears, especially those grown in areas with high humidity and warm springs.

- A slightly extended date of 2017 will benefit consumers and growers alike. The few more seasons of research will enable new products to be tested in both apples and pears in a variety of weather conditions.

- In 2009, about 15% of the total apple area and 40% of the pears (organic and conventional) were treated with streptomycin or oxytetracycline for control of Fireblight, the disease caused by the bacteria *Erwinia amylovora*.[1]

- Experience of pear growers especially in the 2013 season has shown that Blossom Protect has not worked well in the Pacific Northwest or California. It was an unusually warm spring. The copper material that is very promising has been delayed in registration until at least 2014 nationwide and 2015 in California.

Opponents to extending the expiration date of streptomycin say:

- Like most challenges in organic production systems, with fire blight there is no one material and no one practice that will eliminate the problem. Fire blight must be met with a truly organic systems approach that is sensitive to the potential adverse health and environmental effects of inputs and consumer expectations.[2]

- Fire blight resistance to streptomycin is widespread in the United States. Streptomycin-resistant strains of fire blight have been found in California, Oregon, Washington, Michigan, New York,[3] Missouri,[4] and Utah.[5] Plasmid-borne genes have been found to confer resistance in California, Michigan,[6] and New York.[7]

- With regard to the "essentiality" of streptomycin, not all organic apple and pear growers depend on antibiotics. In fact, there is a sizeable proportion of growers of both apples and pears who do not use antibiotics.

- As of March 10, 2011, there were 96 businesses certified as EU-compliant organic producers of apples and/or pears in the state of Washington alone, representing about one third of the state's organic apple and one fourth of the state's organic pear production. EU-compliant organic apple and pear growers cannot use antibiotics, and face a three-year ban from selling in the EU if they do.[8] In addition, cultural changes in the orchard environment have contributed to epidemics of fire blight.[9]

2. Need for phase out of streptomycin

The sub-committee acknowledges the concerns of consumers and previous NOSB members who feel that it is time to phase this material out from organic agriculture. The two positions represented in the discussion section of this document differ on the timing of the phase-out.

Proponents of an extension for streptomycin say:
Because of the need to make sure that this material is phased out, a resolution motion has been added to affirm the commitment by the NOSB to all organic stakeholders. The NOSB must ensure that the decisions made reflect due consideration of the various needs and concerns of the vast array of all our organic stakeholders, especially when dealing with complicated issues, such as this one.

Additionally, in spite of the claims below about the threat of spreading resistance to streptomycin, most of the research on this subject has been conducted with antibiotics used in livestock and very little in orchard environments. Some very recent research specifically for an orchard situation noted that more streptomycin-resistant isolates were cultured from non-sprayed orchards compared to sprayed orchards.[10]

Opponents of an extension for streptomycin say:
Streptomycin is an antibiotic considered by the World Health Organization to be of critical importance to human medicine.[11] Streptomycin is used in a way that exposes bacteria in the orchard to the antibiotic.[12] Current science shows that environmental exposure to antibiotic use in the environment is the major cause of development and spread of antibiotic resistance in human pathogens.[13]The spread of antibiotic resistance does not require contact between the antibiotic and human pathogens because the major means of spreading antibiotic resistance is through the transfer of genes between different bacteria. Uses resulting in low residues (subtherapeutic or subinhibitory levels) can create a high health risk.[14] Streptomycin resistance is evident and expected to grow if urgent use precaution is not exercised.[15] Organic production should not be contributing to the problem of antibiotic resistance.

3. Antibiotic Resistance
Proponents and opponents of extending the expiration date of streptomycin agree that the core issue here is whether there is a risk of enhancing antibiotic resistance in human pathogens. The most astute and experienced scientists in this area realize that science and medicine have to find a way to co-exist with resistance, including managing reservoirs of resistance in the environment and preventing development of new forms of resistance. (Am. Academy of Microbiology, 2009).

Proponents of extending the expiration date of streptomycin say:

- Antibiotic-resistant bacteria that are competent phyllosphere colonisers can persist in the environment, evidently independent of antibiotic use, as shown by Yashiro and McManus (2012). They demonstrated that long-term applications of streptomycin alone did not alter the bacterial communities on apple leaves. They sampled leaves from four orchards that were treated with spring-time applications of streptomycin over 10 years and from four orchards that were not sprayed with antibiotics. The bacterial genera *Massilia*, *Methylobacterium*, *Pantoea*, *Pseudomonas*, and *Sphingomonas* were detected from all orchards, regardless of spray history. More streptomycin-resistant isolates (65%) were cultured from non-sprayed orchards compared to sprayed orchards (50%). They concluded that factors other than streptomycin influence both the proportion of streptomycin-resistant bacteria and phylogenetic makeup of bacterial communities on apple leaves (Yashiro and McManus, 2012).

- There are numerous reports that the use of antibiotics in animal production is associated with increase of antibiotic-resistant bacteria in animals, waste-water, and manure (for some examples see Larsen 2010, Wright 2010). A direct linkage was reported between infection and colonization of humans by antibiotic resistant bacteria from farm animals (Larsen et al 2010). No direct linkage has been demonstrated between antibiotic resistant bacteria in humans and antibiotic sprays on plants (Stockwell and Duffy, 2012).

Opponents of extending the expiration date of streptomycin say:

- Application of streptomycin leads to an increase of streptomycin resistance in the fireblight organism and other bacteria in the orchard.

Selection of bacteria resistant to streptomycin occurs at extremely low antibiotic concentrations.[16] It is accepted that reliance on streptomycin for fireblight control resulted in the development and spread of resistance to streptomycin in *E. amylovora.*[17] Resistance genes are prevalent in treated soils,[18] and researchers have concluded that resistance is often acquired through gene transfer.[19] Some researchers found the highest concentration of streptomycin-resistant bacteria in the phylloplane of treated crops,[20] but Yashiro and McManus (2012)[21] found a higher percentage of cultured phyllosphere bacteria resistant to streptomycin at non-sprayed orchards than at sprayed orchards. But they stated,

> However, our conclusion does not absolve streptomycin of all risk associated with its use. For example, it is possible that streptomycin could select for novel resistance genes in apple orchards, even if the overall frequency of resistant bacteria is not increased. A greater diversity of mobile resistance genes in apple orchards could lead to horizontal transfer of resistance among a greater range of bacteria, which in turn could be consumed on fresh produce.

- Streptomycin resistance genes from the orchard are transferable to other bacteria.

Streptomycin resistance in *E. amylovora* may come from a chromosomal or two known streptomycin resistance genes carried on plasmids.[22] "The carriage of *strA-strB* within an integron, a transposon, and on broad-host-range plasmids has facilitated the world-wide dissemination of this determinant among at least 21 bacterial genera."[23] The streptomycin resistance genes (*strA-strB*) are known to be carried on transposons and spread by horizontal gene transfer, but are unlikely to have been transferred directly –it is more likely that they are spread through intermediate bacteria. "The distribution of the *strA-strB* genes in the environment clearly illustrates the expansiveness of a common microbial gene pool and the rapid dissemination of Ab^r determinants in bacterial populations." [24] This has been confirmed by a several researchers.[25]

- Streptomycin is a critically important antimicrobial.

Streptomycin is classified as a critically important antimicrobial by the World Health Organization. It is a limited therapy as part of treatment of enterococcal endocarditis and Multi-Drug Resistant (MDR) tuberculosis.[26] It is also effective in treating Brucella (brucellosis), Calymmatobacterium granulomatis (donovanosis, granuloma inguinale), Escherichia coli, Proteus spp., Aerobacter aerogenes, Klebsiella pneumoniae, and Enterococcus faecalis in urinary tract infections, Francisella tularensis, Haemophilus ducreyi (chancroid), Haemophilus influenzae (in respiratory, endocardial, and meningeal infections - concomitantly with another antibacterial agent), Klebsiella pneumoniae pneumonia (concomitantly with another antibacterial agent), Mycobacterium tuberculosis, Pasteurella pestis, Streptococcus viridans, Enterococcus faecalis (in endocardial infections - concomitantly with penicillin).[27]

4. Ecological Impacts

Opponents of extending the use of streptomycin say:

- Streptomycin use may have unforeseen ecological impacts.

Since resistance to antibiotics is more prevalent in some groups of microorganisms than others, the dispersal of streptomycin in the environment can disrupt the microbial ecology. For instance, blue-green algae, which are important in sequestering carbon dioxide and releasing oxygen gas, are as a group susceptible to antibiotics.[28]

<u>Differences between Streptomycin and Oxytetracycline</u>

•• Use: While tetracycline is only used during bloom and will only be present on fruit that set early in the bloom period while the late blooms are being sprayed, streptomycin is registered for use from early bloom until 45 days before harvest.

•• Mode of Action: Streptomycin binds irreversibly to bacterial ribosomes and block synthesis of proteins (51). Oxytetracycline binds reversibly to these proteins (McManus et al., 2002). (Category 1, Question 9]

•• Mechanism of Resistance: There are 2 mechanisms of resistance to streptomycin in fire blight bacteria: spontaneous mutation of a chromosomal gene which encodes production of ribosomal protein, thus strep cannot bind to ribosome and bacteria become immune to antibiotic. This is most common in the US. Acquired resistance has been detected occasionally in MI and CA. The pathogen acquired plasmids that contained genes encoding an enzyme that inactivates strep. These resistant isolates of fire blight were detected in an orchard ten years after applications were stopped (34). The fire blight bacteria have not been known to develop resistance to tetracycline in the laboratory, and little is known about the mechanisms for resistance to tetracycline in that bacteria.

** Genetics of Resistance: The genes for resistance to streptomycin that are transferred by plasmid are the same genes known to confer resistance to streptomycin in human pathogens.[29] This is a step in the chain of causation that is not known for tetracycline.

•• Residue on Fruit: While there were not specific studies besides EPA data that set ADI limits that showed residue of tetracycline on fruit, one study in Austrian orchards showed detection of streptomycin residues (33) in apples, with the highest concentrations in the apple core. Apple fruit were collected about three months after bloom and tested for streptomycin. The level of detection was 2 µg/kg (0.002 ppm or 2 ppb) and the limit of quantification was identified as 7 µg/kg (0.007 ppm or 7 ppb). They reported that the highest concentration of streptomycin detected was 18 µg/kg (0.018 ppm), well below the EPA tolerance of 250 µg/kg (0.25 ppm). The Austrian ADI for streptomycin is 0.03 mg per kg of body mass per day (0.03 ppm). The study did not report on exactly what spray practices led to this result.)[Category 1, Question 9]

•• Use in medicine: Both tetracycline and streptomycin are classified as critically important antimicrobials by the World Health Organization. Tetracycline is one of a limited number of therapies for infections due to *Brucella, Chlamydia* spp. and *Rickettsia* spp. Streptomycin is a Limited therapy as part of treatment of enterococcal endocarditis and Multi-Drug Resistant (MDR) tuberculosis. Tetracycline has a higher priority because it is used more frequently for specific uses, which could lead to faster spread of resistance. Tetracycline is administered orally, while streptomycin is administered by injection.[30] It is unclear what link there may be between oral ingestion and the build-up of resistance to injected streptomycin.

Conclusions

Those supporting an extension of streptomycin use say:
There is no evidence that applications of antibiotics to orchards during bloom contributes to antibiotic-resistance in human pathogens. Human pathogens have not been found in orchards and would have to be present for the resistance genes to transfer. Naturally occurring streptomycin resistant bacteria may be minor components of the overall bacterial communities found on apple flowers and in soils, but their presence is independent of the antibiotic application. The amount and timing of the use of this material in an orchard environment does

not contribute to any human health concerns, especially in light of streptomycin being ineffective in humans when ingested orally.

Those opposing an extension of streptomycin use say:
There is evidence that application of streptomycin leads to increase resistance to streptomycin in orchard bacteria, that human pathogens and the fire blight bacteria share the same gene pool of genes resistant to streptomycin (i.e., that the same genes responsible for resistance in *Erwinia amylovora* are also responsible for resistance in human pathogens), that human pathogens do not need to be present in the orchard to obtain resistance genes acquired by and augmented in orchard bacteria, that streptomycin residues are sometimes present in treated fruit, and that streptomycin is still a critically important antimicrobial for use against human pathogens. In light of the crisis of antibiotic resistance, we cannot allow streptomycin use to be extended in organic production.

Evaluation Criteria (see attached checklist for criteria in each category)

	Criteria Satisfied?
1. Impact on Humans and Environment	☒ Yes ☐ No ☐ N/A
2. Essential & Availability Criteria	☒ Yes ☐ No ☐ N/A
3. Compatibility & Consistency	☒ Yes ☐ No ☐ N/A

Substance Fails Criteria Category: NA

Recommended Subcommittee Action & Vote, including classification recommendation (state actual motion):

Classification Motion: Streptomycin is synthetic and is already classified as such on the National List so there is no need to make a motion to that effect.

Listing Motion
Motion to remove the existing expiration date of October 21, 2014 for streptomycin at §205.601(i)(11), and replace it with an expiration date of October 21, 2017, so that the listing reads: (11) Streptomycin, for fire blight control in apples and pears only until October 21, 2017

Motion by: Harold Austin
Seconded by: Zea Sonnabend
Yes: 5 No: 3 Absent: 0 Abstain: 0 Recuse: 0

Additional Motion: **Resolution:** The National Organic Standards Board is committed to the phase out of this material. Between now and the expiration date the Board urges growers and certifiers to include in organic systems plans an annual increase in the extent and/or number of alternative practices and materials that are trialed for controlling fire blight. In addition, the board strongly advocates to USDA a high priority for increased support for research into these alternative practices and materials.

Motion by: Harold Austin
Seconded by: Zea Sonnabend
Yes: 8 No: 0 Absent: 0 Abstain: 0 Recuse: 0

Approved by Jay Feldman, Subcommittee Chair, to transmit to NOSB August 6, 2013

NOSB Evaluation Criteria for Substances Added To the National List: Crops

Category 1. Adverse impacts on humans or the environment? Streptomycin

Question	Yes	No	N/A	Comments/Documentation (TAP; petition; regulatory agency; other)
1. Is there a probability of environmental contamination during use or misuse? [§6518(m)(3)]	X	X		The petition claims the manufacturing process as CBI. However, the 2011 TR (lines 314-315) states, "Dzhedzhev et al. (1975) reported that the manufacture of streptomycin resulted in high atmospheric concentrations of the solvents butyl alcohol and butyl acetate in the workplace." The TR also says (lines 315-332) Streptomycin is produced using fermentation, a process that usually involves the use of solvents and gases that may be discharged into water or air, subject to EPA permits. The TR concludes (lines 326-328) that assuming streptomycin manufacturers comply with applicable water and air regulations; it is unlikely that environmental contamination will result from the fermentation process. (March 8, 2011 TR – lines 326-328) also in that same TR, lines 334-341 states that no surface residue can be found on pear or apple trees after four to six weeks following a spray application(Gardan and Manceau (1984)). Also in this same section the EPA (1988) states streptomycin residues are non-detectable (<0.5ppm) on crops when treated according to label use rates and directions. TR lines 414-415 states that the RED for streptomycin concluded that agricultural streptomycin products, labeled and used according to EPA regulations, will not pose unreasonable risks or adverse effects to the environment (EPA 1992). There is an EPA registration review of streptomycin underway that is scheduled to be completed in 2014.
2. Is there a probability of environmental contamination during, manufacture or disposal? [§6518(m)(3)]	X	X		See above for detailed explanation
3. Does the substance contain inerts classified by EPA as 'inerts of toxicological concern'? [§6517 (c)(1)(B)(ii)]		X		
4. Is there potential for detrimental chemical interaction with other materials used in organic farming systems? [§6518(m)(1)]	X			Streptomycin should not be applied following an application of a Bordeaux mixture and it is incompatible with lime sulfur (according to the 2002 HSDB) (March 8, 2011 TR lines 357 & 358).

5. Is there a toxic or other adverse action of the material or its breakdown products? [§6518(m)(2)]	X	X		March 8, 2011 TR (lines 338) states that strep breakdowns into products that include methylamine, carbon dioxide, and urea, all of which occur naturally in the environment. (EPA 1988, 1992) EPA cited data that showed that streptomycin biodegrades relatively quickly in soil and water. Streptomycin can be phytotoxic to plants; therefore it is sprayed on the surface of plants rather than injected (McManus and Stockwell, 2000). Most apple and pear producers are prudent in their use of streptomycin sprays to reduce costs and to prevent the development of streptomycin-resistant strains of *Erwinia amylovora.* Disease risk models help producers optimize the timing of antibiotic sprays and reduce the total number of applications. These measures can help reduce the development of antibiotic resistance. (March 8, 2011 TR lines 111-115) There is a high probability that streptomycin resistant bacteria are present in the environment as a consequence of pesticidal use of streptomycin (EPA, 2006a). (TR lines 429-431) The HED Chapter of the TRED states that there have been reports of adverse effects resulting from use of streptomycin as a pesticide (EPA, 2006a). (TR lines 449-450) Because of the risk to workers, personal protective equipment is advised to prevent skin contact with streptomycin, and workers are not permitted re-entry into treated areas for at least 12 hours. (TR lines 454-456)
6. Is there persistence or concentration of the material or breakdown products in the environment? [§6518(m)(2)]	X	X		A certain background level of streptomycin is expected in soil due to the natural presence of the bacterium *Streptomyces griseus* (Brosche, 2010). EPA (1988, 1992) cited data that show that streptomycin biodegrades relatively quickly in soil and water. (TR lines 207-210). The breakdown products include methylamine, carbon dioxide, and urea, all of which occur naturally in the environment. Therefore, the application of streptomycin for control of fire blight in apples and in pears in accordance with labeled instructions is unlikely to contaminate the environment. (TR lines 337-341). According to EPA, streptomycin is moderately persistent in aerobic soil (a single value of t1/2= 17.5 days was determined). EPI Suite estimated a shorter aerobic soil half-life (t1/2= 25 days) and a longer sediment half-life (t1/2= 100 days). Given the moderate

				persistence/high mobility and solubility of streptomycin, the chemical is expected to dissipate relatively slowly and at the same time be vulnerable to leaching/run-off. (TR lines 217-225) Gardan and Manceau (1984) reported that no surface residue of streptomycin was detectable on pear or apple trees after four to six weeks following spray application. However, Mayerhofer et al. (2009) showed that the use of streptomycin sprays can lead to detectable concentrations of streptomycin in apples. Streptomycin was detected in 20 of 41 samples from orchards that were treated one to three times with streptomycin sprays. The concentration of streptomycin was highest in the apple cores and skin and ranged from 1.9 to 18.4 µg/kg (equivalent to 0.0019 to 0.0184 ppm, well below the EPA's established tolerance of 0.25 ppm). (TR lines 238-244)
7. Would the use of the substance be harmful to human health or the environment? [§6517 (c)(1)(A)(i); §6517 (c)(2)(A)(i); §6518(m)(4)]	X	X		The TRED for streptomycin concluded that "there is reasonable certainty that no harm to any population subgroup will result from exposure to streptomycin (EPA, 2006b). (March 8, 2011 TR lines 438 – 439) Also, in the TR lines 441-444 states that "Current tolerances (maximum residue limits) for streptomycin on or in apples and pears is 0.25ppm. Assuming that the maximum amount of streptomycin residues are present in all types of food which may contain residues, EPA determined that chronic aggregate dietary exposure from streptomycin residues in food and water is not considered to be a human health concern (EPA, 2006a). Bacterial resistance to streptomycin as a result of pesticidal use has the potential to cause adverse public health consequences if human bacterial pathogens are present in orchards and develop resistance or if non-pathogenic bacteria in orchards develop resistance and later transfer the resistance to human bacterial pathogens. EPA's assessment concluded that "the possibility of antibiotic resistance resulting in adverse human health consequences was of medium concern following occupational application and was of high concern following application by residential users" (EPA, 2006a, pg. 3). (TR lines 645-650) Streptomycin remains important in modern medicine, and an increase in streptomycin-resistant bacteria in

				the environment and in humans may lead to adverse human health consequences. Streptomycin is used today in medicine in combination therapy to treat tuberculosis (due to increasing resistance to other anti-tubercular drugs) and enterococcal endocarditis (when there is resistance to gentamicin). It is also used to treat the plague and tularemia. (TR lines 634-638) See also question #5. Streptomycin is toxic to algae (Qian *et al.,* 2012) and therefore the EPA requires a warning on any streptomycin label include a warning not to apply directly to water or in areas where surface water is present, and to not contaminate water during cleaning of equipment or disposal of wastes. TR lines 414-415 states that the RED for streptomycin concluded that agricultural streptomycin products, labeled and used according to EPA regulations, will not pose unreasonable risks or adverse effects to the environment (EPA 1992). There is an EPA registration review of streptomycin underway that is scheduled to be completed in 2014.
8. Are there adverse biological and chemical interactions in the agro-ecosystem, including biodiversity? [§6518(m)(5)]	X			Toxic to bacteria and algae. See question #7. The ammonium-Nitrogen concentration was significantly increased following application of streptomycin, possibly indicating that nitrifying bacteria were susceptible to this bactericide. This study also found that application of streptomycin at a rate of 3 mg/g soil caused a continuing reduction in the total bacterial population which lasted longer than the study (22 days). Streptomycin applied at 3 mg/g soil also reduced active hyphae only on the first day following application. A broad-spectrum antibiotic like streptomycin would be expected to inhibit the nitrification process in soil. The presence of streptomycin in three different types of soils affected the ecological balance in the soil, causing the elimination of some bacterial populations. The eliminated species were described as beneficial bacteria involved in various metabolic processes, mineralization of organic compounds, degradation of toxic compounds, or creating soil structure. This study also isolated from the soils many strains of bacteria demonstrating resistance to streptomycin, including opportunistic pathogens of humans and/or animals. (2011 TR lines 377-378, 379-382, 386-387, 389-391, 395-398)

				Based on the limited data available, it is still unclear if the use of streptomycin for control of fire blight has significant negative effects on interactions in the agro-ecosystem, including soil organisms. There are no studies available in the field and the studies in the laboratory with soil bacterial populations appear to be contradictory. (TR lines 404-407)
9. Are there detrimental physiological effects on soil organisms, crops, or livestock? [§6518(m)(5)]	X			Toxic to algae. (TR line 347) Algae are present in most of the soils where moisture and sunlight are available, mostly blue-green (Cyanophyta) and green (Chlorophyta). Soil algae are important in maintaining fertility, building soil organic matter, building soil structure, increasing water holding capacity, and aerating soils.[31]

Category 2. Is the Substance Essential for Organic Production? Streptomycin

Question	Yes	No	N/A	Comments/Documentation (TAP; petition; regulatory agency; other)
1. Is the substance agricultural? [§6502(1)]	X			
2. Is the substance formulated or manufactured by a chemical process? [§6502(21)]		X		
3. Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources? [§6502(21)]	X			Streptomycin is a naturally occurring compound which is produced by the soil bacterium *Streptomyces griseus.* Agricultural streptomycin is produced on a large scale by aerobic fermentation of *Streptomyces griseus* followed by isolation and purification by ion exchange (HSDB, 2002; EPA, 1992) March 8, 2011 TR lines 172-174. Also, TR lines 199-200 states that Streptomycin is produced through a naturally occurring process (aerobic fermentation), but the processes used to isolate and purify the substance are not naturally occurring. The forms of streptomycin currently on the National List as approved are listed as synthetic substances.
4. Is the substance created by naturally occurring biological processes? [§6502(21)]	X	X		Streptomycin is a naturally occurring compound which is produced by the soil bacterium *Streptomyces griseus.* Commercially, streptomycin is produced through a naturally occurring process (aerobic fermentation), but the processes used to isolate and purify the substance are not naturally occurring. (TR lines 199-201)

5. Is there a natural source of the substance? [§ 205.600(b)(1)]			X	
6. Is there an organic substitute? [§205.600(b)(1)]			X	
7. Is there a wholly natural substitute product? [§6517(c)(1)(A)(ii)]	X	X		There are several biological control agents (such as bacteria or yeast) that are used to try to outcompete the fire blight pathogen where it occurs on the blossom. These materials are used for fire blight suppression. Two strains of beneficial bacterium, *Pantoea agglomerans,* are: Bloomtime Biological and Blight Ban C9-1. The bacterium Pseudomonas fluorescens A506 is marketed as Blight Ban A506. There are two strains of yeast *Aureobasidium pullulans* that are used to make up the product Blossom Protect (Bio-ferm, Germany) which has recently been introduced into the market to help in controlling fire blight. TR 2011 lines 468-486. In this same TR, Blight Ban A506 is rated as being poor to fair for effectiveness, lines 493-505 (Johnson et al.,2009) in inoculated trials and slightly better in field trials (Johnson 2010). Johnson further states that Bloomtime and Blight Ban C9-1 both performed slightly better with about 50% reduction in disease incidence observed in the inoculated field tests. He rates Bloomtime Biological as poor to good and the effectiveness of Serenade Max and Blossom Protect as fair to good for effectiveness for fire blight suppression. By comparison, the antibiotic treatment oxytetracycline is described as fair to very good, and treatment with streptomycin is poor to excellent (the poor rating is due to widespread pathogen resistance to streptomycin within the western states). (TR lines 493-507) Disease control was more consistent in field trials conducted with compatible mixtures of antagonistic organisms than with single strains –up to 68 and 71% disease reduction on average, compared to 39% and 81% on average, for oxytetracycline and streptomycin, respectively. (TR lines 517-532) In Germany, treatment with Blossom Protect resulted in an average efficiency of 82% reduction in fire blight incidence (results from six different trials). (TR lines 547-548) Johnson (2010) reports that he and his colleagues evaluated Blossom Protect in an

				inoculated fire blight trial in 2008 (also using four applications during bloom). They found this product to be nearly as effective as streptomycin (Agri-Mycin) in an orchard with high disease pressure. (TR lines 552-555) A large amount of public comment received in written form to FR Docket AMS-NOP-12-0070 and verbally at the Spring 2013 meeting indicated that the above "substitute products" did not work well in certain regions or agricultural systems and therefore were not true substitutes.
8. Are there any alternative substances? [§6518(m)(6)]	X			Besides the biologicals, there are alternative substances that are listed as having some control of fire blight and of these oxytetracycline is by far the best alternative substance. Other materials listed are various copper mixtures (a couple of new products currently being looked at by researchers), lime-sulfur, and Peracetic acid (which is as a disinfectant and not as a spray replacement material).
9. Are there other practices that would make the substance unnecessary? [§6518(m)(6)]	X	X		No one practice can eliminate fire blight, including the use of antibiotics. There are practices that can help in reducing fire blight potential in an orchard as part of a systems approach. Some of these would include using fire blight prediction models to assist in proper timing of materials applications, monitoring and removal of infected plant tissue, planting of resistant root stocks (this would only protect the root system and not the fruit producing portion of the tree), ground cover and water management to help reduce humidity levels within an orchard, and also planting of more fire blight resistant cultivars. (TR lines 601-617, 671-701)

Category 3. Is the substance compatible with organic production practices? Streptomycin

Question	Yes	No	N/A	Comments/Documentation (TAP; petition; regulatory agency; other)
1. Is the substance consistent with organic farming and handling? [§6517(c)(1)(A)(iii); 6517(c)(2)(A)(ii)]	X	X		It is currently included on the National List of Allowed and Prohibited Substances, as a synthetic substance allowed in organic crop production for fire blight control in apples and pears only [7 CFR 205.601 (i)(11)] as previously /currently approved by the NOSB and implemented into policy by the NOP. Contrary to consumer expectations. Inconsistent with prohibition on antibiotics in livestock. Inconsistent with European requirements.
2. Is the substance compatible with a system of sustainable agriculture? [§6518(m)(7)]	X	X		If it is used as part of an organic systems plan in a rotational manner, to enhance resistance management in an effort to minimize the potential for resistance to fire blight to develop. Increases likelihood of antibiotic resistance in pathogenic organisms. It is not sustainable because the fire blight organism will develop resistance.
3. If used in livestock feed or pet food, Is the nutritional quality of the food maintained with the substance? [§205.600(b)(3)]			X	
4. If used in livestock feed or pet food, Is the primary use as a preservative? [§205.600(b)(4)]			X	
5. If used in livestock feed or pet food, Is the primary use to recreate or improve flavors, colors, textures, or nutritive value lost in processing (except when required by law)? [§205.600(b)(4)]			X	
6. Is the substance used in production, and does it contain an active synthetic ingredient in the following categories: [§6517(c)(1)(B)(i); copper and sulfur compounds		X		
toxins derived from bacteria	X			
pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals		X		
livestock parasiticides and medicines		X		
production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers		X		

[1] Stockwell, V.O., and Duffy, B., 2012. Use of antibiotics in plant agriculture. Rev. Sci. Tech. Off. Int. Epiz., 31:199-210.
[2] As reported in Ostenson, H.T. 2010. Organic pome and cherry production and marketing issues: Past, present and future. Acta Hort. (ISHS) 873:137-144, and presented to IFOAM, "Over the last ten years, the Hartman Group (Bellevue, Washington, USA) has studied changes in consumer attitudes, backgrounds, and buying characteristics related to the organic market. The Hartman Group surveyed about two thousand household consumers across four regions of the USA. They found that the 'traditional' properties suggested by 'organic' were no longer the same properties held by the new organic consumer. The survey indicated that traditional properties such as 'locally-grown,' Fair Trade, 'tastes better,' and sustainable production ranked at the bottom. The new organic consumers made it clear that they want, plain and simple, a product centered around the 'absence of all health concerns,' and the absence of pesticides, growth hormones, GMO's, antibiotics, and BSE."
[3] McGhee, G. C., Guasco, J., Bellomo, L. M., Blumer-Schuette, S. E., Shane, W. W., Irish-Brown, A., and Sundin, G. W., 2011. Genetic analysis of streptomycin-resistant (SmR) strains of *Erwinia amylovora* suggests that dissemination of two genotypes is responsible for the current distribution of SmR *E. amylovora* in Michigan. Phytopathology 101:182- 191.
[4] Russo, N. L., Burr, T. J., Breth, D. I., and Aldwinckle, H. S., 2008. Isolation of streptomycin resistant isolates of *Erwinia amylovora* in New York. Plant Dis. 92:714-718.
[5] Claudia Nischwitz, Christine Dhiman, 2012. Streptomycin resistance of *Erwinia amylovora*, causal agent of fire blight. Utah State University Extension and Utah Plant Pest Diagnostic Laboratory, PLP-018.
[6] McGhee, G. C., Guasco, J., Bellomo, L. M., Blumer-Schuette, S. E., Shane, W. W., Irish-Brown, A., and Sundin, G. W. 2011. Genetic analysis of streptomycin-resistant (SmR) strains of *Erwinia amylovora* suggests that dissemination of two genotypes is responsible for the current distribution of SmR *E. amylovora* in Michigan. Phytopathology 101:182- 191.
[7] Russo, N. L., Burr, T. J., Breth, D. I., and Aldwinckle, H. S., 2008. Isolation of streptomycin resistant isolates of *Erwinia amylovora* in New York. Plant Dis. 92:714-718.
[8]Instead, these growers rely on a number of other practices, allowing them to avoid fire blight damage to susceptible varieties. Balancing nutrients and avoiding over-application of nitrogen fertilizers, especially on susceptible varieties of apples or pears; avoidance of over-pruning in the dormant season; use of pre-bloom foliar nutrient sprays even though there is no foliage; use of copper materials on the trees between delayed dormant and tight cluster sages as preventive measures against overwintering FB; use of lime sulfur during bloom to thin apples; and, use of Serenade MAX (in the future, perhaps Blossom Protect) post-bloom and at petal-fall, with good spray coverage. (With some differences for pears.)
[9] In response, the following is suggested: Increase species diversity; decrease tree density; use resistant cultivars and rootstocks; plant a variety of cultivars on a variety of rootstocks.
[10] Yashiro, E & McManus, P. 2012 Effect of streptomycin treatment on bacterial community structure in the apple phyllosphere. PLoS ONE 7(5): e37131. doi:10.1371/journal.pone.0037131
[11] WHO, 2009. Critically Important Antimicrobials for Human Medicine, http://www.who.int/foodsafety/foodborne_disease/CIA_2nd_rev_2009.pdf See Table 1.
[12] Streptomycin TR, 2011. Lines 423-431.
[13] American Academy of Microbiology, 2009. Antibiotic Resistance: An Ecological Perspective on an Old Problem. http://academy.asm.org/images/stories/documents/antibioticresistance.pdf (pp.1-5, 10.)
[14] American Academy of Microbiology, 2009. (p.8.)
[15] Streptomycin TR, 2011. Lines 632-633. American Academy of Microbiology, 2009. (p.2.)
[16] Gullberg E, Cao S, Berg OG, Ilbäck C, Sandegren L, et al., 2011. Selection of Resistant Bacteria at Very Low Antibiotic Concentrations. PLoS Pathog 7(7)**:** 1-9.
[17] McGhee, G. C., Guasco, J., Bellomo, L. M., Blumer-Schuette, S. E., Shane, W. W., Irish-Brown, A., and Sundin, G. W. 2011. Genetic analysis of streptomycin-resistant (SmR) strains of *Erwinia amylovora* suggests that dissemination of two genotypes is responsible for the current distribution of SmR *E. amylovora* in Michigan. Phytopathology 101:182-191. Alan L. Jones and Elise L. Schnabel, 2000. The Development of Streptomycin-resistant Strains of *Erwinia amylovora*, in J.L. Vanneste (ed.), *Fire Blight The Disease and its Causative Agent, Erwinia amylovora*, CAB International, UK. Pp. 235-254.
[18] S. Tolba et al., 2002. Distribution of streptomycin resistance and biosynthesis genes in streptomycetes recovered from different soil sites. FEMS Microbiology Ecology 42: 269-276

[19] Egan, S., Wiener, P., Kalli¢das, D. and Wellington, E.M.H. (2001) Phylogeny of Streptomyces species and evidence of horizontal transfer of entire and partial antibiotic gene clusters. Antonie Van Leeuwenhoek 79, 127-133. Wiener, P., Egan, S. and Wellington, E.M.H. (1998) Evidence of transfer of antibiotic-resistance genes in soil populations of streptomycetes. Mol. Ecol. 7, 1205-1216.
[20] George W. Sundin, Dave E. Monks, Carol L. Bender, 1995. Distribution of the streptomycin-resistance transposon Tn*5393* among phylloplane and soil bacteria from managed agricultural habitats. Canadian Journal of Microbiology, 41(9): 792-799.
[21] Yashiro E, McManus PS, 2012. Effect of Streptomycin Treatment on Bacterial Community Structure in the Apple Phyllosphere. PLoS ONE 7(5): e37131
[22] McGhee, G. C., Guasco, J., Bellomo, L. M., Blumer-Schuette, S. E., Shane, W. W., Irish-Brown, A., and Sundin, G. W. 2011. Genetic analysis of streptomycin-resistant (SmR) strains of *Erwinia amylovora* suggests that dissemination of two genotypes is responsible for the current distribution of SmR *E. amylovora* in Michigan. Phytopathology 101:182- 191.
[23] Sundin, G. W. 2002. Distinct recent lineages of the *strA-strB* streptomycin-resistance genes in clinical and environmental bacteria. Curr.Microbiol. 45:63-69.
[24] GW Sundin and CL Bender, 1996. Dissemination of the *strA-strB* streptomycin-resistance genes among commensal and pathogenic bacteria from humans, animals, and plants, Molecular Ecology 5, 133-143
[25] See for example, Cristina Pezzella, Antonia Ricci, Elisabetta DiGiannatale, Ida Luzzi, and Alessandra Carattoli, 2004. Tetracycline and Streptomycin Resistance Genes, Transposons, and Plasmids in *Salmonella enterica* Isolates from Animals in Italy. Antimicrobial Agents and Chemotherapy, 48 (3): 903–908. Alexandre Scherer, Hans-Rudolf Vogt, Edy M. Vilei, Joachim Frey, and Vincent Perreten, 2013. Enhanced antibiotic multi-resistance in nasal and faecal bacteria after agricultural use of streptomycin, Environmental Microbiology 15(1), 297–304. ("This study shows that the application of low concentrations of streptomycin on grass, as occurs during the spraying of orchards, selects for multidrug-resistant nasal and enteric bacterial flora, including extended-spectrum beta-lactamase-producing *E. coli*.") Foster, G. C., McGhee, G. C., Jones, A. L., and Sundin, G. W. 2004. Nucleotide sequences, genetic organization, and distribution of pEU30 and pEL60 from *Erwinia amylovora*. Appl. Environ. Microbiol. 70:7539-7544.
[26] WHO, 2009. Critically Important Antimicrobials for Human Medicine, http://www.who.int/foodsafety/foodborne_disease/CIA_2nd_rev_2009.pdf See Table 1. Tuberculosis is rapidly developing resistance to all known antimicrobials. Phillip Trollip, 2013. Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa. Emerging Infectious Diseases, 19 (3): 449-455 www.cdc.gov/eid
[27] http://www.drugs.com/pro/streptomycin.html
[28] Jose Luis Martinez, 2009. Environmental pollution by antibiotics and by antibiotic resistance determinants. Environmental Pollution 157: 2893–2902.
[29] See, for example, the following articles. C.-S. Chiou and A. L. Jones, 1993. Nucleotide Sequence Analysis of a Transposon (Tn5393) Carrying Streptomycin Resistance Genes in Erwinia amylovora and Other Gram-Negative Bacteria. Journal of Bacteriology, Vol. 175, (3): 732-740. GW Sundin and CL Bender, 1996. Dissemination of the *strA-strB* streptomycin-resistance genes among commensal and pathogenic bacteria from humans, animals, and plants, Molecular Ecology 5, 133-143. McGhee, G. C., and Sundin, G. W. 2011. Evaluation of kasugamycin for fire blight management, effect on nontarget bacteria, and assessment of kasugamycin resistance potential in *Erwinia amylovora*. Phytopathology 101:192-204. Cristina Pezzella, Antonia Ricci, Elisabetta DiGiannatale, Ida Luzzi, and Alessandra Carattoli, 2004. Tetracycline and Streptomycin Resistance Genes, Transposons, and Plasmids in *Salmonella enterica* Isolates from Animals in Italy. Antimicrobial Agents and Chemotherapy, 48 (3): 903–908. Alexandre Scherer, Hans-Rudolf Vogt, Edy M. Vilei, Joachim Frey, and Vincent Perreten, 2013. Enhanced antibiotic multi-resistance in nasal and faecal bacteria after agricultural use of streptomycin, Environmental Microbiology 15(1), 297–304.
[30] WHO, 2009. Critically Important Antimicrobials for Human Medicine, http://www.who.int/foodsafety/foodborne_disease/CIA_2nd_rev_2009.pdf See Table 1.
[31] "Soil microorganism—algae" My Agriculture Information Bank http://agriinfo.in/?page=topic&superid=5&topicid=150
Zancan, S., Trevisan, R., & Paoletti, M. G. (2006). Soil algae composition under different agro-ecosystems in North-Eastern Italy. *Agriculture, ecosystems & environment*, *112*(1), 1-12.