Enhanced Application Technology for Therapeutic Treatment of Huanglongbing (HLB) Infected Commercial Citrus Groves in Florida: Regulatory and Other Considerations

Introduction:

The Florida Citrus Research and Development Foundation (CRDF) has funded research to identify and develop potential agents to provide therapeutic treatment of *Candidatus* Liberibacter asiaticus (*C*Las). This phloem-limited bacterium is transmitted by the Asian citrus psyllid (ACP, *Diaphorina citri* Kuwayama). CRDF efforts through 2015 were described and documented in **The Use of Bactericides in Plant Agriculture with Reference to Use in Citrus to Mitigate HLB** (1). As described in that document, one of the major issues confronted in efficacious treatment regimens is the inability to get foliar applied materials functionally and economically into the vascular system of the infected tree. CRDF has recognized the importance of overcoming this obstacle and funded work on both direct trunk injection and enhanced foliar applications to increase the amount of materials at the sites where the bacteria occurs in the tree. This research was updated and presented to EPA's Office of Pesticide Programs on February 22, 2018 (2).

CRDF also commissioned and sponsored a review of its research programs by the National Academy of Sciences, which was completed and published in early 2018 (National Academy of Sciences, Engineering, and Medicine, 2018. **A Review of the Citrus Greening Research and Development Efforts Supported by the Citrus Research and Development Foundation: Fighting a Ravaging Disease** (3). Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25026.) This document noted the ongoing work on enhancing application methodology across the spectrum of potential *C*las management tools.

As the pressure on the industry has increased with spread of this pest complex to essentially all of the commercial production groves in Florida, with its resulting severe impact on production, interest in expediting these treatment methods has become a high priority for some within the grower community. This interest has been attenuated by the highly variable results associated with use of Oxytetracycline calcium, Oxytetracycline hydrochloride and Streptomycin sulfate as foliar treatments under Section 18 for the past two full seasons. The focus of the industry has now shifted to the potential for trunk injection (4, 5, 6, 7, 8, 9) to increase the efficacy of these antimicrobial agents. Trial work since 2014 has suggested enhanced control activity for

both Oxytetracycline and Streptomycin against *C*Las when injected directly into the trunk of bearing citrus trees. In addition to trunk injections, the use of multiple adjuvants to increase movement through the waxy cuticle has been tested. Other enhancement techniques such as laser ablation (10) has been tested for enhancement of foliar applications and results, to date, indicate the ability to better introduce target compounds into the vascular system via this application methodology.

Regulatory Considerations:

Any technology that increases the amount of a treatment moiety internally in the target site represents potential additional regulatory scrutiny. This is true for products both currently registered and new products or application technologies that have not been subject to EPA registration in the past. Trunk injection is a currently registered method of application in a limited number of food use and ornamental applications and in fact have registrations for use on ornamental citrus varieties (11, 12, 13). The labels that allow trunk injection of antibiotics specifically preclude consumption of fruit from treated trees for at least twelve months (one year after application). Oxytetracycline has labels for use via trunk application. When permanent tolerances are established for the active ingredient, the primary concern would be whether direct injection increases the residues in the fruit above those associated with foliar applications. Secondary issues include the translation of dosages from field-level broadcast foliar application into efficacious doses when direct application into the vascular system of the plant is accomplished.

Foliar uses of antibiotics are currently authorized for use on citrus under Federal Insecticide, Fungicide and Rodenticide Act, Section 18 provisions for use of non-federally registered active ingredients to meet an urgent non-routine emergency. This action is supported by time limited tolerances for oxytetracycline and streptomycin that expire on December 31, 2019 (14, 15). Full federal registration for these actives are pending with EPA. When full registration is granted, a traditional tolerance will be established and will be the measurement benchmark limit for residues of the products when used via trunk injection or other enhanced application method.

Typically, once an active ingredient that is subject to a Section 18 is federally approved the Section 18 is rendered moot. However, in this case, in a telephone call to FDACS in mid-September, EPA's Section 18 Lead, Tawanda Maignan, noted the unique circumstances covered by our Tree Health Section 18. EPA indicated that when Section 3 registrations are obtained for individual active ingredients the remaining product use labels subject to Section 18 would remain in place. This does raise a question of the differences in the pending Section 3 label conditions compared to the use patterns currently allowed under the Section 18 labels.

With registration, the final approved tolerance will be established which may be different from the temporary tolerances in place for streptomycin and oxytetracycline. Once the Section 3 registration is approved the Section 18 route for an application method change for that active is not available (unless specifically waived by EPA). The correct labelling route would be a label amendment under normal Section 3 registration procedures or possibly a SLN to add the use for a specific geographic region or state if circumstances warrant such a label.

Limited preliminary information suggest that efficacious residual levels may be maintained for longer period at higher levels when products are directly introduced into the phloem stream. While this would indicate the potential for longer-term activity when applied in this manner, it also raises the question of duration of residual product and the impact of sequential treatments. One currently proposed use pattern would be injection of an antibiotic immediately after harvest to provide the longest interval between application and potential harvest of the subsequent crop. While this may work for some varieties, where bloom occurs prior to harvest with essentially two crops on the tree at the same this potential for increased residues creates another set of concerns and issues.

Other Considerations:

Prior to development of proposed labelling and registration activity, the value and economics of such uses must be determined and characterized. The data generated needs to fulfil two purposes: 1) the purely scientific, to guide the decision process on how and when to use the technology; and 2) regulatory, to guide the approval review process. The process elements required for the two types of data are not the same. Data utilized to determine the labelling and use patterns necessary to maximize efficacy can be done outside of the regulatory process under basic standard operating procedures that guide scientific enquiry. Data developed in support of regulatory decisions must meet statutory guidelines for Good Laboratory Practice (16) as defined in the Code of Federal Regulations. The GLP standards require much more detailed records and documentation than studies done in most academic settings and would require more resources to develop. Typically, these registration data development efforts are overseen by a Study Director (as defined under the regulations). The Study Director has significant liability associated with study design, execution, documentation, and archiving under EPA's GLP regulations in order to meet the compliance standards. This responsibility is subject to audits by EPA Enforcement personnel and carry significant civil penalties if not done correctly. There are a limited number of contract laboratories that can provide this level of process management.

The scientific underpinning of the decision to pursue registration, such as the currently funded CRDF research projects, are important and would be considered supplemental data when utilized in the regulatory process. They cannot replace the required Part 158 Guideline Studies (17). For a label use expansion to include the direct introduction of an active moiety into the phloem of infected citrus trees, the appropriate data package must be complete and submitted to EPA with the appropriate fee under the Pesticide Registration Improvement Act (PRIA) (18). These fees vary based on the decision action sought and necessary EPA review requirements to reach a decision. At a minimum, the impact on existing or proposed tolerances for the active ingredient would be required.

Within the potential range of moieties that may be subject to any enhanced application technology, the data set necessary for registration ranges from a complete registration package to a limited package of residue data to support expansion of a currently registered use. Before an informed estimate of data generation can be made, a comprehensive set of studies to establish effective dose rates and timings needs to be done.

As has been discussed in relation to the temporary tolerances for foliar applications associated with the Section 18's currently in place for oxytetracycline and streptomycin, the global marketing impacts of residues on markets must also be considered. Major global markets for fruit, juice and other byproducts have indicated a lack of willingness to establish MRLs in support of antibiotic use in plant or animal agriculture. This reticence would lead to the need for data development to ensure safe entry into these markets through management of timing of any applications via this technology. The regulatory standard for entry into some countries is the lowest level of detection whether it can be quantified or not. This level of concern results in large measure from consumer pressure directed toward international brands and retailers, not regulatory standards set by governmental processes.

Options:

The potential for increased efficacy and resulting higher level of control of the *C*las pathogen in infected groves would indicate the need to pursue the regulatory approval of these technologies for near-term industry support. To best frame the issue for data development, EPA's Office of Pesticide Programs should be engaged to discuss the limited information CRDF and the industry have on hand in this area and to solicit the Agency's input on pathways necessary for registration in the shortest time possible.

Among the short-term efforts that could be made, whether directly by CRDF, a registrant or other party to expedite this process, are:

- Small-scale (crop destruct) trials using the registered tree injection oxytetracycline materials to further define use parameters such as tree size related dosing and timing.

- Initial residue testing in fruit and byproducts using standard practice for registered ornamental truck injection materials with sample collection and residue analysis under GLP analytical protocols (crop destruct).

- Rate definition studies to determine targeted treatment populations, age, size and level of infection levels (crop destruct).

If CRDF is involved in funding Part 158 Guideline studies to support EPA registration, the data generated in direct support of registration should be submitted directly to the Agency by CRDF to maintain data protection under the FIFRA registration process.

It would be my recommendation that a project manager with expertise overseeing FIFRA registration activities be identified to serve as the Study Director for any project involving Guideline data. This does not have to be CRDF staff.

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11) Arbor-OTC, Injectable Tree Antibiotic Label, EPA Reg No. 74578-7, 39.6% Oxytetracycline hydrochloride,, Arborjet, Inc., 99 Blueberry Hill Road, Woburn, MA 01801

12) Terrier™ Systemic Antibiotic Label, EPA Reg No. 69117-10, 4.3% Oxytetracycline hydrochloride, Arbor Systems, P. O. Box 34645, Omaha, NE 68154

13) Tree Tech OTC Label, EPA Reg No. 64014, 4.57% Oxytetracycline Calcium Complex, Florida Silvics, Inc. 950 SE 215th Avenue, Morrison, FL 32668

14) FR Vol 82, No. 46, March 10, 2017, 40 CFR, Part 180: [EPA-HQ-OPP-2016-0539], Oxytetracycline: Pesticide Tolerances for Emergency Exemption, Government Printing Office; http://www.regulations.gov Docket Identification Number EPA-HQ-OPP-2016-0539 pp 13245 – 13251.

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