Policy and Regulatory Issues for Gene Drives in Insects

WORKSHOP REPORT

Sarah R. Carter and Robert M. Friedman, *J. Craig Venter Institute, La Jolla, California*

Workshop organizers, Ethan Bier, *UC San Diego* and Robert Friedman, *J. Craig Venter Institute*

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Workshop Participants

We are very grateful to each of the workshop participants for their participation, varied perspectives, and insights.

Zach Adelman, Virginia Tech
Omar Akbari, UC Riverside
John Bauer, UC San Diego
Ethan Bier, UC San Diego
Cinnamon Bloss, UC San Diego
Craig Callender, UC San Diego
Sarah R. Carter, J. Craig Venter Institute
Adriana Costero-Saint Denis, National Institute of Allergy and Infectious Diseases
Peter Cowhey, UC San Diego
Genya Dana, U.S. Department of State
Brinda Dass, Food and Drug Administration
Jason Delborne, North Carolina State
Mary Devereaux, UC San Diego
Peter Ellsworth, Legler Benbough Foundation
Robert M. Friedman, J. Craig Venter Institute
Valentino Gantz, UC San Diego
Clark Gibson, UC San Diego
Bruce Hay, California Institute of Technology
Mark Hoddle, UC Riverside
Anthony A. James, UC Irvine
Stephanie James, Foundation for NIH
Lyric Jorgenson, NIH Office of Biotechnology Activities
Michael Kalichman, UC San Diego
John Marshall, UC Berkeley
William McGinnis, UC San Diego
Jack Newman, Defense Advanced Research Project Agency
Alan Pearson, USDA Animal Plant Health Inspection Service
Hector Quemada, Danforth Center
Larisa Rudenko, Food and Drug Administration
Anthony Shelton, Cornell University
Joseph Vinetz, UC San Diego
Jennifer Weisman, Defense Advanced Research Projects Agency
Brenda Wong, former UC San Diego
Chris Wozniak, Environmental Protection Agency

The views and opinions expressed in this report are those of the authors and not necessarily those of the institutions at which they work, the other participants at the workshop, or the organizations that funded the study. The authors assume full responsibility for the report and the accuracy of its contents.

Introduction

In March 2015, two UC San Diego scientists demonstrated the first experimental application of a new gene editing technology, CRISPR-Cas9, to "drive" a desired trait throughout a population of fruit flies (Gantz and Bier, 2015). In November 2015, the UC San Diego scientists, collaborating with a group at UC Irvine, developed a method to quickly drive an anti-malarial gene throughout a population of mosquitos (Gantz et al., 2015). This so-called "gene drive[1]," rather than following the usual rules of inheritance, could be used in principle to spread the desired trait—i.e., preventing mosquitos from transmitting the parasite that causes malaria—throughout a mosquito population in one or two seasons.

The next month, another group of scientists in the United Kingdom demonstrated that a similar gene drive approach could be used to drive down mosquito populations to levels predicted to no longer support the transmission of malaria (Hammond et al., 2016). Slightly more than 1% of the estimated 3000 mosquito species carry this pathogen, yet despite the extensive global effort to control them, these few species are responsible for 500 million cases of malaria and an estimated 0.5 to 1 million deaths per year.

Other researchers are working to apply gene drives for controlling agricultural insect pests, for example, to control a destructive cousin of the harmless fruit fly (spotted wing fly), which causes about $0.5 billion annual loss in soft fruit production in the Western U.S. (Bolda, et al., 2010) or to control the insect that transmits citrus greening disease, responsible for about $0.5 billion per year loss of orange juice production in Florida (Alvarez, et al., 2016). Genetic engineering methods (but not yet gene drives) are also being applied to control Diamondback moth, a pest to vegetables in the cabbage family, estimated to be causing $4 to $5 billion per year of damages worldwide (Zalucki, et al., 2012).

The benefits are clear if these research efforts are successful; however, the risks must first be carefully evaluated. When gene drives are used to modify an insect species, they have the potential to permanently change the characteristics of a population. When used to suppress a species, they have the potential to eliminate the species from a local environment.

The key difference between gene drives used to modify a species and earlier generations of biotechnology is the intended persistence of a genetically engineered (GE) trait in the environment; gene drive insects are effective because they mate with wild populations of insects and preferentially pass on GE traits to future generations. When used for population suppression, gene drives are not expected to persist in the environment indefinitely, but could in principle cause some harm to the environment either from unintended consequences of the gene drive itself or from impacts related to the elimination of a local species (such as ecological impacts that harm non-target organisms). The most important challenge in moving the technology out of the lab will be for developers, risk assessors, and other stakeholders to work together to ensure that data and information useful to identifying and characterizing hazards and exposure are generated and evaluated, risks are estimated and mitigated, and decisions are made based on open and engaged discussions.

On January 20–21, 2016, the J. Craig Venter Institute and UC San Diego held a 2-day workshop in San Diego, CA, titled, "Gene Drives to Control Insect-Borne Human Disease and Agricultural Pests: A Workshop to Examine Regulatory and Policy Issues." This workshop brought together scientists working to apply gene drive technologies to insects with federal regulators, ecologists, ethicists, and environmental policy analysts. Also included were experts in laboratory biosafety, insectary standards and operation, field trials of GE insects and more traditional biocontrol organisms, and relevant international treaties and protocols.

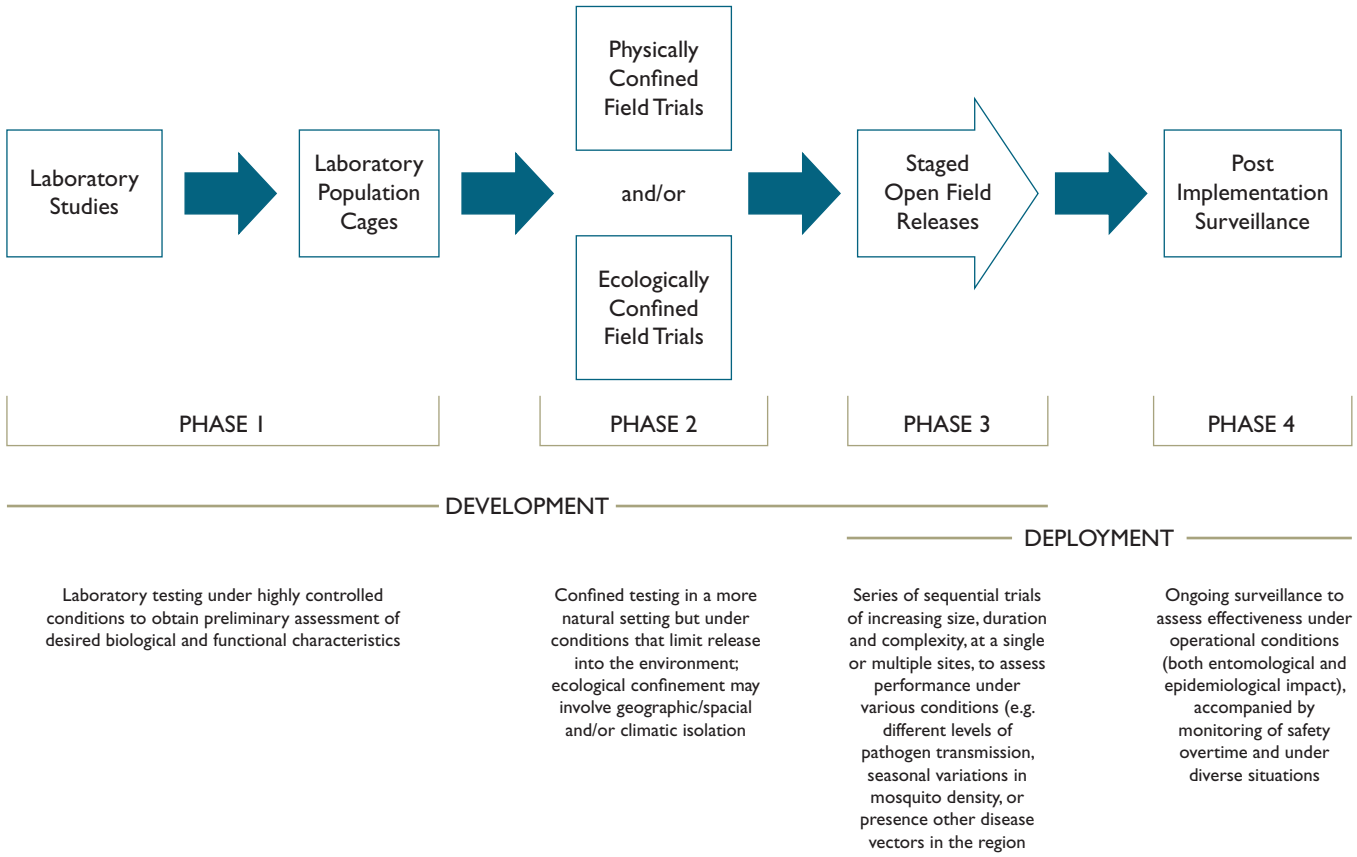
1 Traditionally, the term "gene drive" has been used to describe a process whereby a gene or trait is preferentially driven through a population. However, the term has increasingly been used to describe a genetic construct that enables gene drive, a usage that we embrace in this document for simplicity (though it should be noted that some genetic constructs may allow gene drive only under certain conditions). Throughout this document, we refer to insects engineered to contain gene drive constructs as "gene drive insects."

The participants identified and discussed the key challenges and hurdles that both scientists and decision makers will face as scientists work to develop gene drive insects intended for eventual release into the environment (the agenda is found in the Appendix). We separately considered each step of the phased testing pathway proposed by the World Health Organization (WHO) for testing GE mosquitoes (which it calls "genetically modified" or GM mosquitoes), starting with laboratory containment, then moving to physically contained field trials (i.e. field cages), ecologically confined field trials, and finally to stages of release (WHO-TDR and FNIH, 2014; see Figure 1). At each step, we explored the experience to date, the regulatory and risk assessment needs, and gaps in our knowledge or regulatory structures that would need to be filled before a new gene drive insect could be deployed safely.

In addition, the group considered challenges that technology developers will face in earning public trust and acceptance of the technology, even beyond regulatory compliance and risk mitigation. Workshop participants repeatedly emphasized the need for early, robust, and ongoing engagement with the communities where these insects might be released, starting with the earliest field testing (including field cages).

As important context for the discussions, we often reflected on experience to date with GE insects that do not contain gene drives, GE animals more broadly, and other technologies used to achieve similar goals (e.g., biological control and traditional pesticides). We paid particular attention to how these technologies have been addressed by regulatory agencies and the extent to which different stakeholders have accepted their use. Embedded in these conversations was an understanding that gene drive insects are likely to face all of the regulatory and societal challenges of these previous products, but due to their intended persistence in the environment, to an even greater extent. Given the promise

Figure 1: Phased testing Pathway for Genetically Modified Mosquitos. Redrawn from WHO-TDR and FNIH, 2014.



of these new technologies, however, workshop participants were committed to charting a realistic path forward and identifying the action items necessary to make progress.

On June 8, 2016, the National Academies of Science, Engineering, and Medicine released a report on responsible conduct in the development and testing of gene drives (NAS, 2016). Our January workshop was conducted independently of that process (although one of the workshop participants also served on the NAS committee). The action items listed below represent an accounting of our workshop with some additional research and analysis motivated by the discussions. Box 1, found on page 17, includes a summary listing of the action items throughout the document.

Key Action Items from the Workshop Discussions:

The goal of the workshop was to identify, if possible, a path to successful application of a gene drive technology to control insect-borne human disease or agricultural pests, fully realizing that such a path may not be possible. Participants were urged to suggest "action items" needed to encourage progress towards a successful outcome or to remove impediments along the way. We have organized these suggestions into the following categories: 1) suggestions for researchers and research funders, 2) suggestions for U.S. regulators and policy makers, and 3) suggestions for the international community.

Throughout this workshop report, specific suggestions are identified with the following symbol "**»**" and with text in ***bold italics***.

1. Suggestions for Researchers and Research Funders

Workshop participants identified a series of suggestions and recommendations directed towards the research community itself. First, given that new gene and genome editing approaches have greatly expanded the capabilities of molecular biologists to engineer new traits and functions, the participants explored ways to harness these new capabilities to tailor safer and more appropriate products for particular applications. Second, the participants stressed the importance for the researchers to recognize responsibilities beyond the science itself and regulatory approval. In particular, participants stressed the importance of active local community engagement during the field testing stages, including cage trials in ecologically compatible environments. Third, participants identified the need for guidance documents to inform the research community and regulators about best practices for moving from the lab to field trials. Each of these is discussed below.

A. Gene Drive Technologies and Products

Though gene drives have most often been characterized in the press as a single technology, the opening session of the workshop explored the wide variety of approaches under development, each with particular strengths and weaknesses for meeting a variety of goals and needs. Current approaches fall into two broad categories (Champer, et al., 2016): 1) modification drives, i.e., a gene drive designed to spread a genetic modification throughout a population (e.g., to prevent the transmission of a human or plant parasite) and 2) suppression drives, a gene drive designed to reduce or eliminate the targeted insect.

Within each category, different technical approaches are possible, also with differing characteristics. For example, some technical approaches have greater specificity (reducing possible "off-target" effects within a species or "non-target" effects, the chance of affecting other species). Some will rapidly penetrate through a population, needing only a small number of GE insects to induce changes. Others will require the introduction of large numbers of insects to achieve the desired goal, thus reducing concerns from the accidental release of just a few. Some approaches may be removable from the population by re-introducing large numbers of wild-type insects. Some methods may be more resistant to

selective pressures that will reduce the effectiveness of the engineered trait over time. Scientists are also working on ways to disable already introduced gene drives by using a second gene drive in the event that the first drive exhibits unanticipated and undesired consequences.

A key theme that emerged at the workshop was: "Now that new and more powerful gene editing technologies allow us to design (almost) anything we want, what do we want to design?" This discussion led to the identification of two key action items:

» ***Support Research to Develop New and Varied Gene Drive Technologies.***

Workshop participants pointed out that although the recent success of CRISPR-Cas9 based gene drives is impressive, the technology is still at an early stage of development. Other methods may have preferable characteristics for some specific applications. Research funders, as well as the research community itself, would be well advised to explore multiple strategies.

For example, Table 1 below, redrawn from Champer, et al. (2016), lists a range of available gene drive systems, in various stages of development, and their attributes. This table is included to illustrate the variety of approaches being explored; the list is by no means exhaustive. CRISPR-Cas9 based approaches are one example of "homing-based drives." These homing-based drives spread very quickly and efficiently; modeling predicts that only a few individual insects may be necessary to

Table 1: Comparison of the various types of gene drive systems. Redrawn from Champer, et al. (2016)

	Home-based drive	X-Shredder	Medea	Toxin-antidote underdominance	Chromosomal rearrangement	*Wolbachia*
Type	Either	Suppression	Replacement	Replacement	Replacement*	Replacement†
Rate of spread	Fast	Moderate	Moderate	Slow	Slow	Moderate
Locally confined?	No	No	No, if low fitness cost‡	Yes	Yes	No, if low fitness cost‡
Resistance allele generation rate	High	Low	Low	Moderate	Very Low	Unknown
Reversible?	Yes	Yes	Yes	Yes	Yes	No
Removable with wild type?	No§	No§	No, if low fitness cost‡	Yes	Yes	No, if low fitness cost‡
Status	*Drosophila*, *Saccharomyces*, *Anopheles stephensi*, *Anopheles gambiae*	Incomplete in *Anopheles gambiae*	*Drosophila*	*Drosophila*	Natural examples	Field tests

The characteristics listed here are variable and depend on a range of factors (for example, ecology of the target species, population distribution, movement patterns, fitness costs, payload characteristics, and so on); therefore, only ideal-case scenarios are compared to emphasize intrinsic differences of the various types of drives. *Chromosomal rearrangement can be used for short-term population suppression. †It is possible that male-killing strains of *Wolbachia* may be usable for population suppression. ‡High fitness costs may make these systems locally confined and removable with the release of large numbers of wild-type organisms. §Suppression types that proceed to fixiation and eliminate a population will remove the gene drive system, allowing replacement with wild-type organisms.

ensure that the trait is propagated into and throughout an entire population.

Other types of gene drives may be threshold-dependent, which might be a desirable characteristic for some applications. Such drives require many individuals with the drive (for example, up to and above 50% of the total number in the wild population) to ensure that the GE trait is driven into the population. Modeling suggests that threshold-dependent drives that are released at numbers below the threshold will be selected out of the population over time while those released in quantities above the threshold will eventually be propagated throughout the population (Marshall and Hay, 2012).

» ***Design Applications to Meet Multiple Objectives using the Full Range of Gene Drive Technologies.***

Throughout the course of our discussions, it became apparent that for any specific application to be successful, a gene drive insect would have to be engineered to meet multiple needs and objectives. Designing for a successful health outcome or control of an agricultural insect pest alone is not sufficient. In addition, developers must design for safety for both human health and the environment, regulatory approval, social acceptability, and affordability, simultaneously and from the beginning.

The first step, of course, is to be able to move from the laboratory to field testing (from phase 1 to phase 2 and phase 3, as shown in Figure 1 above). No insect engineered with a gene drive insect yet been tested outside of physical containment. While CRISPR-based gene drives and other homing-based drives might eventually be preferred due to their more rapid rate of spread, some participants suggested that regulators or local communities might prefer early tests of gene drive insects with more moderate rates of spread or those that are capable of being removed from the ecosystem by re-introducing wild type varieties. Characteristics can vary even when using similar molecular tools. CRISPR-based drives designed to modify a population to prevent transmission of disease will likely be maintained in the environment longer than CRISPR-based suppression drives, which may lead to population crashes and the ultimate loss of the gene drive from the wild (Adelman and Tu, 2016).

More experience will be needed before researchers can determine what type of gene drive is most appropriate for a given application and stage of development or deployment. Participants stressed that in addition to understanding the ecology and possible impacts and risks of the gene drive insect itself, it will also be necessary to take into account other factors for field test site selection, such as the regulatory environment and acceptance of the local community (Ramsey, et al., 2014).

Researchers will also have to consider post-implementation monitoring (stage 4 in Figure 1) and possibilities for risk mitigation in the initial design of the gene drive insect. Reversal technologies (i.e., those that can be used to remove a gene drive insect that has already been deployed) may be desirable in case of an unintended consequence or unwanted persistence in the environment. However, workshop participants were skeptical that regulators would rely on such technologies for risk mitigation because they too may present new unknown risks.

B. Community Engagment

Throughout the workshop, it was very clear that community engagement at many levels should be an important part of any successful deployment of a gene drive insect. Regulatory compliance is necessary for responsible development of these technologies, but it is not sufficient. Most regulatory systems throughout the world (including the one in the U.S.) are science-based and have a very limited capacity to evaluate or weigh non-physical harms, cultural preferences, or ethical considerations. Because gene drives are more likely to interact with and persist in the environment than most products of biotechnology deployed to date, the workshop participants felt that gene drive developers have a greater responsibility to pursue social acceptance of the technology beyond just regulatory approval:

» *Incorporate Community Engagement Activities as a Critical Component of Field Testing.*

Perhaps the strongest consensus to emerge during the workshop was the need to incorporate community engagement activities for field testing (including field cage trials) and later stages of release. Such engagement would necessarily come well before specific plans are made, and the resulting conversations would be an important factor in determining where and how such releases are conducted.

Several participants discussed the need for, and advantages of, forming multidisciplinary teams to effectively accomplish this, including gene drive researchers and technology developers alongside social scientists, communications experts, and others. Participants also stressed that funders must be aware that community engagement activities will be critical for successful deployment of gene drive technologies and thus need to provide adequate funding for such activities in addition to the scientific research itself.

C. Guidance Documents on Best Practices

One session at the workshop was devoted to a review of existing guidance documents relevant to insect gene drive research and field testing, as well as the need for updates or additional guidance given the speed with which the technology is advancing. Some of these guidance documents have been prepared by regulatory agencies and such international bodies as WHO, and will be discussed in later sections of this report. However, much of the guidance about best practices has been assembled by committees within scientific societies or independent groups of scientists convened by research funders. Workshop participants suggested the need to update several of these guidance documents as well as the importance of developing additional guidance for community engagement to support these activities:

» *Review and Update Existing Non-governmental Guidance Documents.*

The most extensively used guidance for working with GE insects in laboratories (phase 1 of Figure 1) was prepared by a non-governmental organization, a committee of the American Society of Tropical Medicine and Hygiene (ASTMH, 2003). The ASTMH Arthropod Containment Guidelines outline containment procedures for all GE insects, but do not address the question of whether, and if so how, insects engineered to contain gene drives might be assessed and handled differently. Participants suggested that ASTMH undertake a review of these Guidelines, explicitly considering research on gene drives, and revise them, if needed.

Recently, more than 20 leading gene drive researchers collaborated on and published a Policy Forum in Science on ways to safely conduct gene drive experiments in the laboratory (Akbari, et al., 2015). (Four of the workshop participants were coauthors.) The Policy Forum included discussions of physical containment methods and possible strategies for biological containment as well. Such efforts at information sharing are vital for rapidly advancing research fields, and publication in journals such as Science can help regulators develop their own guidance documents.

Another helpful guidance document is "Guidance for Contained Field Trials of Vector Mosquitoes Engineered to Contain a Gene Drive System: Recommendations of a Scientific Working Group" (Benedict, et al., 2008). (Two workshop participants were also in that Working Group.) As the title indicates, the document addresses contained field trials (phase 2 of Figure 1), but was written prior to the existence of "strong" gene drives such as those recently made with CRISPR-Cas9 systems. Similar to the other guidance documents, this Guidance should be reviewed explicitly considering recent advances, and revised, as needed. A similar effort focusing on best practices for open field trials (phase 3) and post-implementation surveillance (phase 4) of gene drive insects will be needed if and when products advance to that stage of testing.

These guidance documents (as well as those discussed below) will need to be revisited and revised on a regular basis as new gene drive technologies are developed and

more experience is gained in conducting laboratory experiments and field trials.

» *Develop Guidance for Community Engagement.*

Workshop participants identified a critical need for a guidance document outlining best practices for community engagement. Participants discussed case studies of successful community engagement, including one in Australia (Kolopack, et al., 2015) and a second in Mexico (Lavery, et al., 2010). Key lessons included starting early in the technology development process, prior to outlining specific plans for field testing; respecting community members' input and addressing anxieties directly; and expecting to dedicate a significant amount of time to the effort. Researchers may also be able to learn from other types of community engagement, including, for example, processes related to deployment of traditional pesticides, both for agricultural purposes and for vector control.

In addition to developing guidance for best practices for community engagement, participants discussed the need for a common ethical framework for understanding what constitutes community consent or approval for field testing or deployment of gene drive insects. Consensus in a large community is usually unattainable, and talking with every individual is often impossible. Other proxies for approval can be useful (e.g. government endorsement or majority support from an elected body), but their value will depend on the circumstances within that community. Under what conditions can a researcher feel confident proceeding with a trial or release?

2. Suggestions for U.S. regulators and policy makers

In the U.S., regulatory oversight of GE insects varies by both stage of research and by the characteristics of the insect. For laboratory research (phase 1 of Figure 1), any researcher in an institution that receives federal funds must follow containment guidelines issued by the National Institutes of Health (NIH, 2016). If they are working with a nonindigenous plant pest insect, they must also comply with quarantine guidelines developed by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS, 2002).

Field trials and eventual deployment in the environment are likely to be regulated by either APHIS or the Food and Drug Administration (FDA) under the Coordinated Framework for the Regulation of Biotechnology (OSTP, 1986). The USDA's Animal and Plant Health Inspection Service (APHIS) regulates plant pest insects, insects used for biological control of weeds and plant pests, and animal pest insects, regardless of their GE status. FDA is likely to regulate all other GE insects. Each agency has its own set of procedures and standards for regulatory decision making; both also have to comply with the procedural requirements of the National Environmental Policy Act (NEPA), which requires environmental assessment of any major federal action (such as a permit or approval).

Workshop participants identified a series of suggestions, summarized below, for U.S. regulators and policy makers regarding both laboratory research and subsequent field trials and deployment.

A. Suggestion for NIH

Because gene drives (especially highly efficient CRISPR-based gene drives) may persist in the environment after release of just a few individual insects, preventing unintentional release from the laboratory into the outdoor environment is critical. As mentioned above, the research community has published voluntary guidance for containment of GE insects (the ASTMH Arthropod Containment Guidelines; ASTMH, 2003) and a group of leading gene drive researchers has published their opinions about best practices for safely conducting laboratory experiments with gene drives (Akbari, et al., 2015). Though quite helpful, participants pointed out that neither held the authority of government-issued requirements, such as the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines; NIH, 2016).

Institutions that receive U.S. federal funding must comply with the NIH Guidelines for laboratory research involving genetic engineering or risk losing all federal funding. These

Guidelines are implemented primarily through local Institutional Biosafety Committees (IBCs) made up of researchers at each institution with varying expertise plus community members and others. All research involving recombinant or synthetic DNA must be reviewed by the IBC to ensure biosafety for the researchers themselves and to prevent release into the environment. The vast majority of proposals reviewed by most IBCs are focused on human pathogens; many IBCs do not have the necessary expertise to determine adequate containment measures for gene drive insects. To date, scientists conducting research on gene drives have been proactive in proposing protocols to ensure containment, but because CRISPR-Cas9 has made development of gene drive technologies much easier, more scientists are likely to pursue them and may face unprepared IBCs.

Workshop participants offered a suggestion for NIH:

» ***Develop Additional Guidance as part of the NIH Guidelines for Laboratory Experiments Using Gene Drives.***

The current NIH Guidelines include specific containment requirements for a long list of organisms and types of experiments. NIH could provide additional guidance specific to experiments using gene drive insects that could help inform IBCs about the procedures and protocols that IBCs should follow to review such experiments and for researchers to follow. The responsibility for review and approval would remain with the local IBC.

A very precautionary option, which was proposed but received little support by the participants at the workshop, is that NIH could require that work with gene drive insects be evaluated at a level above the IBCs and the institution. Only a few classes of experiments are reviewed nationally, for example, certain types of gene transfers into human research participants. Workshop participants felt that working with gene drives in laboratory containment, under carefully specified conditions (i.e., following guidance suggested above) did not pose the same level of risk as those that currently require national level review.

B. Suggestions for the Office of Science and Technology Policy

As mentioned above, the U.S. regulates biotechnology for release and commercial use based on the Coordinated Framework for the Regulation of Biotechnology, which was first developed in 1986 by the White House Office of Science and Technology Policy (OSTP, 1986). A key tenet of the Coordinated Framework is that products of biotechnology should be regulated based on the type of product and not based on how it was produced. As a result, since 1986, biotechnology products have been regulated based on a patchwork of statutes and regulations that cover different types of products and risks. Under the Coordinated Framework, as it is applied today, there are different regulatory pathways and procedures for GE insects that are plant pests (overseen by APHIS) and those that are not (overseen by FDA). These agencies often consult with each other, the Environmental Protection Agency (EPA, which has regulatory authority for pesticides), as well as other federal agencies. Workshop participants had two overarching suggestions for OSTP in its oversight of the Coordinated Framework:

» ***Establish a "Single Door" Approach to the Biotechnology Regulatory System.***

A product developer would have a single office or point of contact in the U.S. government that would determine the regulatory pathway for their product, thereby reducing the uncertainty and time spent in navigating the variety of potential paths that a product could take.

» ***Clarify the Roles of the Regulatory Agencies.***

The workshop participants expressed some confusion about the regulatory system and the reasoning behind FDA's role in the regulation of GE insects. In particular, there was discussion of whether EPA's authorities over pesticides would be better suited to gene drive insects intended for suppression of insect populations; in fact, some researchers have referred to such gene drives as "genetic insecticides." Furthermore, gene drive insects that are plant pests may be subjected to a very different process (at APHIS) than those that are not plant pests (at FDA). OSTP should clarify the reasoning behind the distribution of regulatory responsibilities and work to

ensure that similar products undergo similar levels of scrutiny when evaluated by different agencies.

C. Suggestion for FDA

GE insects that are not plant pests are likely to be regulated by the FDA; because engineering an insect changes the structure or function of the animal, FDA will consider it to be an animal drug[2] and will regulate it based on its authorities under the Federal Food, Drug, and Cosmetic Act. FDA's experience in regulating GE animals under these authorities has been limited, with only three product approvals. FDA recently released a draft environmental assessment for public comment for the first GE insect to be regulated by the agency, a GE mosquito from the company Oxitec (FDA, 2016). Although these mosquitoes are not gene drive insects, they are intended to interact with and drive down populations of wild mosquitoes.

Each of the GE animal applications that has gone through the regulatory process at FDA has been subject to a process specific to that product, as the agency considers each application on a case-by-case basis. Gene drive insects are likely to be no different. However, there are several aspects of gene drive insects that may challenge FDA's procedures. A key action item for FDA:

» ***Clarify how the Regulatory Process might Incorporate a Staged-Release Approach, including Environmental Assessments.***

FDA should clarify how it might oversee a staged-release approach, including how and when environmental assessments will be required under NEPA.[3] The GE animals approved to date have been grown only in confined settings and have not required field tests. The Oxitec mosquitoes currently under review at FDA (which are not gene drive insects) are the first GE animals to undergo an environmental assessment under NEPA for field trials, before a new drug application is submitted for approval. For gene drive insects, multiple field trials of varying physical containment and ecological confinement may necessitate multiple environmental assessments. Furthermore, although FDA has issued a preliminary "finding of no significant impact" on the investigational field trial of the Oxitec mosquitoes (FDA, 2016), whether it will be able to do so for any gene drive insect is unclear. The agency may want to consider what would be required for a more extensive environmental impact statement if and when a gene drive insect is ready for even a small-scale release, including guidance on relevant risk questions and mitigation practices that the agency will want product developers to consider.

D. Suggestions for USDA/APHIS

Plant pest insects that are engineered to contain gene drives will be regulated in the U.S. by APHIS under the Plant Protection Act of 2000. APHIS has applied these authorities to biotechnology primarily in the context of GE plants, which are often engineered using plant pest vectors. Over the past twenty years, APHIS has overseen thousands of field trial releases of GE plants each year and the full deregulation of, in total, about 120 GE plants (i.e. GE plants that can be cultivated in the environment without oversight) (APHIS, 2016a).

To date, APHIS has issued open release permits (for field testing only) for two GE insects (neither of which contain gene drives): the pink bollworm, for which the agency developed a full environmental impact statement under NEPA (APHIS, 2008), and the diamondback moth. APHIS issued a "finding of no significant impact" on the environment and approved field trials for the diamondback moth in 2014 (APHIS, 2014); trials in field cages were conducted in 2015,

2 The relevant definitions of a "drug" include the intent to alter the structure or function of the body of an animal, OR to diagnose, cure, treat, or prevent disease.

3 Under the National Environmental Policy Act (NEPA), any significant federal action, including field trial permits and product approvals, triggers an Environmental Assessment (EA). In many cases, an EA has yielded a Finding of No Significant Impact (FONSI) and the agency will continue with its regulatory process, reaching decisions based on its statutory authority. If the agency cannot issue a FONSI (i.e. if the EA shows some significant environmental impact), then it must develop a much more extensive Environmental Impact Statement (EIS). In general, product developers work with the regulatory agencies to agree to terms that will limit the environmental impact, secure a FONSI, and avoid an EIS. Because gene drive insects have intended impacts in the environment (sometimes including persistence of engineered traits), it will be interesting to see if a field trial or approval can warrant a FONSI by either APHIS or FDA.

and open field trials are planned for 2016. While most GE plants undergo a deregulation process when moving toward full scale deployment and commercialization, as mentioned above, it is not clear that GE insects will do so as well. Instead, they may remain under permit, with each release requiring a new permit from APHIS and therefore a new environmental assessment under NEPA.

Two suggestions for APHIS are:

» ***Develop a Framework for Staged Field Testing and Deployment of Gene Drive Insects.***

APHIS's extensive history with GE plants and more limited history with GE insects have given the agency valuable experience in assessing GE organisms for impacts on the environment. However, the permitting evaluations undertaken by the agency to date have focused on confinement: limiting persistence of the organism and its engineered traits in the environment. Such a paradigm was developed and tailored for GE crop plants, and the agency will face a challenge reviewing gene drive insects that have intentional and persistent interaction with the environment. APHIS may need to develop a risk assessment framework for permitting field trials that is based on estimated environmental risk rather than solely on the adequacy of confinement. While this may represent a new way of thinking at APHIS and may require updated regulations, its statutory authority does not preclude such a framework.

The agency's long-standing program overseeing biological control programs should be of help. APHIS's experience with non-GE biological control organisms (e.g., parasitoids that kill the eggs of the emerald ash borer) far exceeds its experience regulating GE insects. Because such biological control organisms are intended to persist in the environment and many are used to control populations of wild insects, they may be the best analog for some GE plant pest insects containing gene drive constructs. Environmental assessments for biological control programs can be found on the agency's website (APHIS, 2016b). By our count, the programs approved by APHIS include 22 insects released to control plants (weeds) and another 12 released to control plant pest insects.

The development of a framework for gene drive insects can draw on the agency's previous experience both with GE insects (such as the GE diamondback moth) and with non-GE biological control organisms. As part of this framework, the agency might consider issuing guidance that would include the agency's expectations for data collection, monitoring, and mitigation procedures at each step in the process, for example, when conducting field cage experiments, small-scale field trials, etc. Such guidance would allow product developers to pursue technologies that are most likely to satisfy APHIS's requirements.

» ***Evaluate and, if Necessary, Update Laboratory Containment Guidelines.***

As mentioned above, APHIS maintains "Containment guidelines for nonindigenous, phytophagous arthropods and their parasitoids and predators" and inspects laboratories where such organisms are kept (APHIS, 2002). APHIS may want to evaluate how well these guidelines accommodate gene drive insects. In addition to considering gene drives inserted into nonindigenous plant pests, the agency may also want to weigh the possibility of expanding the guidance (or the definition of "nonindigenous") to indigenous plant pest insects engineered to contain gene drives.

3. Suggestions for international organizations

Although much of the development of gene drive insects will take place in the U.S. and other developed countries, many of the products will have applications in the developing world. Decisions to allow testing and eventual use will be the responsibility of regulators in each country, but international agreements or organizations also play important roles in the governance of GE insects. Two in particular have been most active: the Cartagena Protocol on Biosafety of the Convention on Biological Diversity (Cartagena Protocol) and the World Health Organization (WHO), in particular the WHO

Special Programme for Research and Training in Tropical Diseases (WHO-TDR).

The Cartagena Protocol addresses GE organisms broadly. WHO focuses on GE insects for controlling insect-borne human diseases. Two other international organizations might play useful roles in the governance of gene drive insects in the future, but are not active yet on this topic. The International Plant Protection Convention (IPPC) is a multilateral treaty addressing plant health and protection, including damage by insect plant pests. The World Organization for Animal Health (OIE) addresses insect-borne animal diseases.

In addition, bilateral and regional organizations might also play useful roles. For example, the North American Plant Protection Organization has issued guidance for testing GE insect plant pests (which does not account for GE insects that will persist in the environment; NAPPO, 2007) and pan-African organizations have organized regional insect pest eradication programs.

A. Suggestions related to the World Health Organization

WHO-TDR has a long history developing guidance documents and training on the use of GE mosquitoes as a means to control insect-borne disease such as malaria and dengue fever. A second organization, the Vector Control Advisory Group (VCAG), is an advisory body to WHO on new forms of vector control methods to control insect-borne disease, and recently considered modified mosquitoes.

» ***Review Existing WHO-TDR Guidance and Training Documents***

WHO-TDR has been actively engaged in developing guidance for testing and implementation of GE mosquitoes for close to 15 years. The 2014 "Guidance Framework for Testing of Genetically Modified Mosquitoes" (WHO-TDR and FNIH, 2014) is the most thorough and detailed guidance available on the topic. The following year, WHO-TDR issued a biosafety training manual for potential use of GE mosquitoes, based on courses previously offered in Africa, Asia, and Latin America in 2008 through 2011 (WHO-TDR, 2015). Again, given the prevalence of diseases such as malaria and dengue in developing countries, participants stressed the importance of both preparing documents about best practices for evaluating and testing potential uses of these new technologies, as well as capacity building (e.g., training, institutions) necessary for effective use.

Though both WHO-TDR documents discuss gene drives, they were prepared prior to the recent developments of highly efficient CRISPR-based gene drives in two mosquito species. Workshop participants suggested that the 2014 Testing Guidance be reviewed in the context of these new developments and updated, if needed. In particular, those sections on contained field trials (phase 2 in Figure 1 above) and staged open field trials (phase 3) should be reexamined to see if additional guidance is needed for these next generation gene drives. For example, given the greater chance of persistence in the environment, additional remedial precautions may be required. Developing guidelines for monitoring persistence of gene drive insects in the environment was another area of need identified by the workshop participants. This guidance should be revisited periodically as experience is gained and new technologies are developed.

» ***Continue and Expand Review of GE mosquitoes by VCAG***

In 2013, WHO established a Vector Control Advisory Group (VCAG) on New Tools to serve as an advisory body to WHO on new forms of vector control for malaria and other vector-borne diseases. At the time of our workshop, VCAG had met four times and had not yet issued any opinions on GE insects. However, in March, 2016, in response to the Zika virus outbreak, WHO convened a special meeting, at which two technologies relevant to gene drives were considered: a GE mosquito developed by Oxitec that does not employ gene drive as part of the construct and a Wolbachia (bacterial) based biocontrol method that essentially functions as a non-GE gene drive (and which is included in Table 1 above). VCAG recommended "the carefully planned pilot deployment under operational conditions of [both technologies] accompanied by rigorous independent monitoring

and evaluation," but not full-scale deployment at this time (VCAG, 2016).

VCAG has established a process where scientists and product developers can bring new technological approaches to VCAG for review and seek advice on the types of data needed for their evaluation for subsequent recommendation. Though the VCAG process was only briefly discussed at our workshop, given recent developments, it appears to be an important new, independent review mechanism for novel GE approaches such as the gene drive approaches presented in Table 1.

B. Suggestions related to the Cartagena Protocol

The Cartagena Protocol (CBD, 2000) is the primary international agreement related to GE organisms (which it calls "living modified organisms"). Its goal is to ensure the safe handling, transport, and use of GE organisms that may have adverse effects on biological diversity and risks to human health. With regard to GE insects, it has two roles: first, through the Protocol's Biosafety Clearing House, it provides guidance and training for developing country regulators on risk assessment of GE organisms, in general, including some specific guidance for risk assessments of GE mosquitoes. Second, the Protocol specifies a series of measures that signatories (Parties) must follow for intentional and unintentional transboundary movements of GE organisms.

» ***Rely on WHO to Develop Detailed Guidance on Risk Assessment of GE Mosquitoes***

Several workshop participants pointed out that other international organizations may have greater resources and expertise for developing the type of detailed guidance and training needed for assessing gene drive insects. The risk assessment guidance prepared under the auspices of the Cartegena Protocol Ad Hoc Technical Assessment Group on Risk Assessment (CBD, 2012) is quite general and introductory in nature. Though it does contain a chapter on GE mosquitoes, it does not include the depth of information in the WHO-TDR documents, which include, for example, detailed discussion of best practices for early stage testing of GE insects in the field. In addition, several nations with mature biotech industries are not signatories to the Protocol, including the United States, Canada, Australia, and Argentina. Under the rules of the Protocol, experts from these nations with the greatest experience regulating GE organisms can participate only as observers in the development of the Guidance.

The Guidance itself anticipates that more detailed information and training may be needed: "Since this guidance is not focused on one particular type of technology or genetic mechanism, additional and more specific guidance may be necessary when conducting the risk assessment of a particular LM [living modified] mosquito depending, among other things, on the strategy used. The risk assessment of LM mosquitoes performed on a case-by-case basis may also benefit from a broader approach using laboratory and confined field tests together with mathematical modeling."

As discussed above, WHO already has a well-developed and detailed framework for evaluating and testing GE mosquitoes (which workshop participants suggested should be reviewed and updated as needed), as well as a training manual for use in developing countries. Additional efforts devoted to helping developing countries evaluate gene drive insects may be more effective if led by WHO, rather than under the Cartagena Protocol.

» ***Encourage Use of Bilateral, Regional, and Multilateral Agreements among Parties for Field Trials or Releases where the Risks of Transboundary Movement may be Significant.***

The Protocol's principal focus is on transboundary movement of GE organisms. For gene drive insects, the possibility of transboundary movement is a significant consideration, in particular, for large-scale field trials or releases.

The Protocol anticipates using "bilateral, regional and multilateral agreements and arrangements" for intentional transboundary movements of GE organisms (Article 14). Several workshop participants supported use of such agreements for testing and use of gene drive insects for unintentional transboundary movement, as well, in particular, among countries that want to move

forward with trials or applications and where there may be a significant risk of transboundary movement.

» ***Encourage Additional Institutions and Organizations to Assist Parties to Develop the Regulatory Capacity and Processes Needed to Regulate GE Organisms, including GE Insects.***

The Protocol leaves the regulation of GE organisms to each country individually, consistent with their internal laws and regulatory structures. However, several workshop participants pointed out that many of the developing countries that might benefit most from, for example, use of GE insects for control of vector-borne human disease, do not currently have regulatory systems with the ability to adequately review proposed field testing or applications. In addition, they stressed that field trials of such technologies should only be conducted in places with the scientific and governance capacity to adequately assess and oversee the experiments (Brown, et al., 2014). The Protocol recognizes the importance of regulatory "capacity building" (Article 22), especially for developing-country Parties, however, progress has been slow. A recent review by the Protocol's Liaison Group on Capacity-Building for Biosafety (CBD, 2016) noted that only about half of the Parties had fully implemented national biosafety frameworks and urged Parties that have not done so to put in place biosafety legislation "as a matter of priority."

Workshop participants strongly supported regulatory capacity building for developing countries with an interest in using GE insects, but felt that this task was too large for the limited resources and expertise of the Convention on Biological Diversity to handle on its own. Indeed, Article 22 of the Protocol itself envisions assistance from other global and national institutions and organizations, including the private sector. Though the workshop participants did not identify specific organizations to help in this regard, they did recognize the importance of engaging the expertise from nations with mature biotechnology industries to help evaluate and improve the technical regulatory capabilities within developing countries that are considering the use of these new technologies.

Box 1: Summary of Action Items

In January, 2016, the J. Craig Venter Institute and UC San Diego convened a workshop to examine the regulatory and policy issues associated with the use of gene drive insects to fight human disease and agricultural pests. The task given to participants was to identify a path, if possible, to safely move gene drive insects from the laboratory to field trials, and if appropriate, to eventual deployment. Below are the action items identified by participants to encourage progress and remove barriers toward that end.

Suggestions for Researchers and Research Funders

I. Regarding gene drive technology development and products that might employ them:
- Support research to develop new gene drive technologies with varied characteristics.
- Design applications to meet multiple objectives using the full range of available (and to be developed) gene drive technologies.

II. Community engagement:
- Incorporate community engagement activities as a critical component of field testing.

III. Guidance documents on best practices:
- Review and update existing non-governmental guidance documents.
- Develop guidance for community engagement.

Suggestions for U.S. Regulators and Policy Makers

I. For the National Institutes of Health (NIH):
- Develop additional guidance as part of the NIH Guidelines for laboratory experiments using gene drives.

II. For the Office of Science and Technology Policy (OSTP):
- Establish a "single door" approach to the biotechnology regulatory system.
- Clarify the roles of the regulatory agencies.

III. For the Food and Drug Administration (FDA):
- Clarify how the regulatory process might incorporate a staged-release approach, including environmental assessments.

IV. For the US Department of Agriculture's Animal and Plant Health Inspection Service (USDA/APHIS):
- Develop a framework for staged field testing and deployment of gene drive insects.
- Evaluate and, if necessary, update laboratory containment guidelines.

Suggestions for International Organizations

I. For the World Health Organization (WHO):
- Review and update existing WHO guidance and training documents.
- Continue and expand review of GE mosquitoes by the Vector and Control Advisory Group (VCAG).

II. Related to the Cartagena Protocol:
- Rely on WHO to develop detailed guidance on risk assessment of GE mosquitoes.
- Encourage use of bilateral, regional, and multilateral agreements among parties for field trials or releases where the risks of transboundary movement may be significant.
- Encourage additional institutions and organizations to assist parties to develop the regulatory capacity and processes needed to regulate GE organisms, including GE insects.

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Appendix: Workshop Agenda

Gene Drives to Control Insect-Borne Human Disease and Agricultural Pests: A Workshop to Examine Regulatory and Policy Issues

Wednesday, January 20

8:30–9:00 Continental Breakfast

9:00–10:00 Goals for the Workshop; Introductions
Session leads: Bob Friedman, Ethan Bier
All participants

10:00–11:00 Overview of the Technology; Status of the Research
Session lead: Adrianna Costero
Resources: Ethan Bier, Valentino Gantz, Bruce Hay, Stephanie James, Tony James, Jack Newman

11:00–11:15 Break

11:15–12:30 Existing Guidance Documents for GM Insects
Session Lead: Stephanie James
Resources: Zach Adelman, Tony James, Alan Pearson, Tony Shelton

12:30–1:30 Lunch

1:30–2:30 Laboratory Containment
Session lead: Zach Adelman
Resources: Omar Akbari, Brenda Wong, Lyric Jorgenson

2:30–3:30 Physically or Ecologically Confined Field Trials; Staged Open-Field Releases
Session lead: Tony James
Resources: Tony Shelton, Joe Vinetz

3:30–3:45 Break

3:45–4:30 Lessons from Traditional Biological Pest Control
Session lead: Mark Hoddle
Resources: Tony Shelton

4:30–6:00 U.S. Regulation of GM Insects
Session lead: Sarah Carter
Resources: Brinda Dass, Alan Pearson, Larissa Rudenko, Jennifer Weisman, Chris Wozniak

6:30 Reception and dinner at UC San Diego Faculty Club

Thursday, January 21

8:30–9:00 Continental Breakfast

9:00–10:00 International Frameworks, Cartagena Protocol
Session lead: Hector Quemada
Resources: Genya Dana, Clark Gibson, Stephanie James, John Marshall

10:00–11:00 Information Needs: Modeling and Risk Assessment
Session lead: John Marshall
Resources: Bruce Hay

11:00–11:15 Break

11:15–12:15 Community Engagement; Informed Consent
Session lead: Cinnamon Bloss
Resources: Jason Delborne, Mary Devereaux, Tony James, Mike Kalichman, Hector Quemada

12:15–1:15 Lunch

1:15–3:00 Key Conclusions and Next Steps
Session leads: Ethan Bier, Sarah Carter, Bob Friedman
Resources: All Participants

3:00 Adjourn

About the Authors and Workshop Organizers

Sarah R. Carter, Ph.D.

Dr. Carter is the Principal at Science Policy Consulting LLC where she focuses on societal and policy implications of emerging biotechnologies with an emphasis on helping inform policy makers and facilitate decision making. Until April, 2016, she worked in the Policy Center of the J. Craig Venter Institute, where she led influential projects on the challenges synthetic biology creates for policy makers. Previously, Dr. Carter was a policy analyst at the White House Office of Science and Technology Policy (OSTP) where she focused on issues relating to climate change and sustainability. She is also a former AAAS Science and Technology Policy Fellow and a former Mirzayan Fellow of the National Academies. She earned her Ph.D. in Neuroscience from the University of California-San Francisco.

Robert M. Friedman, Ph.D.

Dr. Friedman is Vice President for Policy and University Relations at the J. Craig Venter Institute. He directs JCVI's Policy Center. Prior to joining the Venter Institute, Dr. Friedman was Vice President for Research at The Heinz Center, a nonprofit environmental policy research organization. Earlier, he was a Senior Associate at the Office of Technology Assessment, U.S. Congress (OTA). For 16 years, he advised Congressional committees on issues involving environmental and natural resources policy. Dr. Friedman received his Ph.D. from the University of Wisconsin-Madison, in Ecological Systems Analysis. He is a Fellow of the American Association for the Advancement of Science (AAAS).

Ethan Bier, Ph.D.

Dr. Bier is a professor in the section of Cell and Developmental Biology at UC San Diego, studying the basic biology of fruit flies as well as using the common fruit fly to study mechanisms of human disease. Dr. Bier's group recently developed a new CRISPR-Cas9 based method referred to as "active genetics" that greatly biases transmission of genetic traits, thereby bypassing traditional constraints of Mendelian inheritance. One application of this new technology is to create gene drive systems for disseminating anti-malarial effector genes into mosquito populations. Dr. Bier received his Ph.D. from Harvard Medical School and did his postdoctoral studies at UCSD. He assumed a faculty position at UCSD in 1990. He is an Alfred P. Sloan and Basil O'Connor Scholar and an Allen Distinguished Investigator.