GeneWatch UK comments on WHO/FNIH Guidance Framework for Testing of Genetically Modified Mosquitoes

January 2013

This is a copy of a response to an online survey is designed to provide input into the first public consultation on a guidance framework to provide quality standards for assessing the safety and efficacy of genetically modified (GM) mosquitoes for malaria and dengue control, available on: http://www.who.int/tdr/news/2012/submit_comments/en/index.html

Background questions
Please provide some background about yourself. You do not need to identify yourself personally, all responses are confidential. The following questions are designed only to understand the specific questions and comments by type of group.

1) Select the primary area you represent (even if you represent more than one, please select only the role from which you are responding to this consultation) (Reset)

International health/research organization (?)

2) Have you provided technical input into this document earlier? (Reset)

No

3) Select your current geographic region (these are WHO regions) (Reset)

European Region

4) Country of Nationality
UK
Nationality
British

5) How did you hear about this consultation?
Colleague

6) Please add the details of how you heard about this consultation (name of LISTSERV, title of journal, etc.)

Consultation questions
7) Is there a specific topic that has drawn you to comment on this consultation? If so, please state what this is and why.

GeneWatch UK was contacted by individuals and NGOs in other countries for information about UK company Oxitec in 2009. Since then, we have researched the company and its activities in considerable detail and have published a number of briefings, available on our website at: http://www.genewatch.org/sub-566989

Our concerns about releases of GM mosquitoes conducted by Oxitec to date – including the company's failure to publish full risk assessments for consultation, seek fully informed consent, or meet transboundary notification requirements - are summarised in:

Oxitec's Genetically Modified Mosquitoes: Ongoing Concerns. GeneWatch UK. August 2012. http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf . Many scientific references relevant to this consultation are included in this briefing.

Our response to publication of Oxitec's results in the Cayman Islands is in this press release: GeneWatch UK PR: GM mosquito trial results in Cayman pour cold water on claimed benefits.10th September 2012. http://www.genewatch.org/article.shtml?als[cid]=566989&als[itemid]=571139

Our concerns about Oxitec's relationship to Syngenta and its role in developing regulatory processes are summarised in a joint NGO briefing:
Genetically-modified insects: under whose control? GeneWatch UK, Testbiotech, Berne Declaration, SwissAid, Corporate Europe Observatory. November 2012.
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Regnbrief_fin2.pdf

GeneWatch UK has also responded to the European Food Safety Authority's consultation on its draft guidance for environmental risk assessment of GM animals (which includes GM insects):
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/EFSA_GWresponse.pdf
.

8) Are there any key issues that you believe are not identified and/or addressed in this document? If so, please explain.
Yes.

1. There are no Declarations of Interest or indications of how WHO-TDR/FNIH selected the experts involved: no steps appear to have been taken to prevent conflicts of interest from biasing the guidance framework.
2. The authors have not identified who is the regulator for assessment of efficacy. The lack of a regulator for efficacy is a fundamental problem compared to other approaches such as vaccines.
3. The idea that benefits should be taken into account has wrongly been subsumed into the biosafety chapter. Risk assessment does not include efficacy assessment and benefits should not be claimed by applicants before efficacy has been established. A separate chapter should have been included outlining who the customer is likely to be and how the risk assessment, efficacy assessment, alternatives, standards of care, and cost-effectiveness analysis might be combined to reach a decision at each stage.
4. The reversibility of self-limiting approaches is not guaranteed because environmental responses may not be linear e.g. if another mosquito species occupies the ecological niche vacated by the suppressed species and disease incidence increases as a result, this might not be reversed by stopping releases of GM mosquitoes. This error is repeated throughout the document.
5. Computer models are misused to imply that benefits of GMM releases are predictable: yet these models oversimplify the complex relationships between disease vectors, pathogens, ecosystems and humans, and omit mechanisms which might cause harm (e.g. increases in other vectors, loss of immunity or cross-immunity, pathogen evolution, development of resistance). There is no discussion of model validation or how alternative conceptual models can be developed and due diligence undertaken to reach a more credible view of the balance of benefits and risks, taking into account uncertainties and possible unknowns.
6. A highly over-optimistic view of the current state of development of the self-sustaining approach is provided.
7. Disadvantages of GMM approaches are not listed.
8. Risks and potential benefits are context-dependent and may depend, for example, on the presence or absence of the target species and target disease and presence or absence of

other non-target disease vectors. Yet there is no discussion in the document of how approvals for releases might be restricted to certain receiving environments. Spread of GM insects via human movement (e.g. on clothing or in tyres etc.) may be particularly important.

9. Physically-confined testing is always needed prior to open releases and it is disingenuous to suggest otherwise (i.e. Phase 2 testing should not be defined in such a way as to allow so-called "ecologically confined" testing to replace caged trials). This proposal appears to be a post-hoc justification for Oxitec's behaviour rather than a genuine attempt to meet regulatory or ethical requirements or protect human health and the environment. A clear distinction should be made between regulatory requirements for "contained use" and for "deliberate release" of GMOs.
10. Lack of an adequate baseline or insufficient understanding of vector-ecosystem-human-pathogen interactions should be cited as a possible reason not to proceed to the next phase. Failure to acknowledge complexity, limits to knowledge and uncertainties, is a major omission from the document.
11. There are numerous missing risk assessment issues, such as: the need to avoid releasing non-native strains and to assess strains for disease transmission properties; the potential for partial reduction of mosquito density in dengue endemic areas to increase the incidence of dengue hemorrhagic fever (DHF); the possibility that pathogens will evolve in response to reduced vector transmission; the potential for increased disease burden from non-target vectors.
12. The role of the Guidance Framework in relation to other draft risk assessment guidance is unclear. It is surprising that practically no reference has been made to the work on drafting guidance for GMM already done under the auspices of the Convention on Biological Diversity (pages 43-51): http://www.cbd.int/doc/meetings/bs/mop-06/official/mop-06-13-add1-en.pdf . Draft guidance for environment risk assessment of GM insects by the European Food Safety Agency (EFSA) is also under development but has received many critical comments during consultation. This guidance will be critical not only in the EU but also for exports of GM mosquito eggs from the EU, because a risk assessment meeting EU standards must accompany exports for open releases (the UK has been the country of export for all GMM eggs for open release to date). If the WHO/FNIH publishes guidance which conflicts with this EU guidance it risks establishing lower standards for developing countries and/or misleading potential customers about the standards required by companies based in the EU which wish to export GMM products.
13. The Guidance fails to recognise that long-term effects such as evolution of resistance or evolution of pathogens are not just a monitoring issue. Failure to consider these thoroughly during the decision-making process could lead to irreversible adverse effects and might be regarded as lack of due diligence.
14. The Guidance fails to specify explicit requirements for transparency, consultation and access to justice and there is no reference to the Aarhus Convention which sets international standards in this area.
15. There is only limited recognition of transboundary issues in the document (which also apply to so-called self-limiting approaches).
16. The document makes a weak and frankly unacceptable argument for abandoning requirements for fully informed consent prior to conducting open releases. Apart from breaching ethical requirements, this will cause practical problems because people will not be informed that they are taking part in an experiment which may not work and which carries risks until the point at which data is collected from them (especially for health surveillance purposes). They may then ask why they were not fully informed at earlier stages when they were exposed to comparable risks. Failure to fully inform people who may be affected by the trial may also have legal implications and affect the liability of the research team for any harms should they arise.

17. There is a complete absence of any discussion of liability for adverse effects on health or the environment and the importance of due diligence.
18. The document continues to cite uncritically the USDA APHIS' EIS which has been severely criticised in the scientific literature and has now been abandoned as the basis for decision-making in the USA, following a critical report by the USDA Office of Inspector General in 2011.
19. Claims in Chapter 5 that regulators should "acknowledge the potential health benefits rather than relying on a precautionary approach" are in flat contradiction to established legal standards in most countries and fail to acknowledge that claimed benefits may not exist (i.e. the efficacy of GMM has not been established).
20. The lack of any "lessons learned" from past practice (including the absence of a public report from the controversial Mosqguide project).
21. The limited discussion of alternatives and failure to identify or address disadvantages to the GMM approach.

It is particularly difficult to understand why the working group continues to work closely with Oxitec when this company has conducted open releases in the Cayman Islands, Malaysia and Brazil with:

- No standard of care provisions
- No prior caged trials in relevant ecosystems
- No baseline data on ecosystems, target species or disease
- No published risk assessments (except a summary in Malaysia) and no consultation on risk assessments (except in Malaysia)
- No published experimental protocols
- No monitoring plans, emergency plans or licence conditions (except in Malaysia)
- No fully informed consent
- A number of false, misleading and untested claims, including that the releases are a "solution" to dengue (e.g. in a widely-publicised jingle used in Brazil); that the released GM mosquitoes are "sterile"; and that Oxitec's RIDL technology is "better than SIT" (a claim which has never been tested, let alone established)
- A deliberate decision to use a country with no biosafety law (the Cayman Islands) for the first releases and not to inform the public that the mosquitoes were genetically modified
- A deliberate decision to press ahead with releases in Brazil prior to the adoption of risk assessment guidance for GM insects (which was then under development) and to request that the risk assessment remained confidential
- Failure to report export notifications to the UK and EU authorities (which is required under EU law)

Such behaviour falls far short of "best practice" and should not be endorsed as such by the World Health Organisation or the FNIH.

Additional note: The use of the term GMM to mean genetically modified mosquitoes (although used for convenience in these comments) is potentially confusing as it is commonly used to mean GM micro-organisms.

9) Do you find the document clear and helpful enough for countries to develop their own regulations about genetically-modified mosquitoes?

No. The document is inadequate and needs to be substantially re-written. Conflicts-of-interest need to be removed. The document's main purpose seems to be to get the WHO to adopt measures proposed by commercial influences which undermine existing regulatory and ethical requirements,

rather than to provide guidance to potential customers for GMM on what these requirements are. The document includes proposals to:

1. Include claimed benefits in risk assessments: this is not the purpose of a risk assessment and conflicts with legal definitions;
2. Blur the line between contained use and deliberate open release of GMOs by inventing a new category of "ecologically confined" trials which are not treated as open releases despite being open releases: this proposal is not compatible with existing biosafety requirements;
3. Remove the requirement for an independent ethics committee and the requirement to obtain informed consent from people living in areas with GMM trials: this is not compatible with Helsinki Declaration requirements and previous reports on this issue by the WHO;
4. Ignore or undermine transboundary notification requirements mandated by the Cartagena Protocol on Biosafety to the Convention on Biological Diversity;
5. Ignore or undermine international provisions for access to environmental information and environmental justice (Aarhus Convention);
6. Avoid any discussion of how releases of GMMs will be restricted to the receiving environments for which they have been authorised;
7. Undermine the precautionary principle and ignore uncertainties and ignorance about the behaviour of complex environmental systems (including interactions between humans, vectors and pathogens).

COMMENTS ON FOREWORD

Para 2 on page x: the references provided for the need for "new tools" are focused on malaria not dengue. Many experts argue that much more could be achieved with the proper implementation of existing tools for dengue. Public health approaches should also be mentioned: e.g. improved water supplies can also help eliminate the need for standing water and reduce the incidence of dengue; better surveillance and prompt treatment also makes a significant difference. The successes of the Roll Back Malaria programme should also be mentioned: http://www.rbm.who.int/globaladvocacy/pr2011-09-12.html .

It is incorrect to state that the risk incurred by testing new and unproven strategies must be evaluated against the risks posed by the status quo (final paragraph on page x). The process of decision-making requires a risk assessment for open releases of GMOs, which is a legal requirement in most countries. This risk assessment has a specific purpose which does not include assessment of benefits, but which may include risks which could arise due to poor efficacy of the intervention (as well as other risks). Subsequent decision-making must then take account of additional information, including the assessed efficacy of the proposed intervention, the availability of alternatives, cost-effectiveness and broader social and economic aspects. The limits of knowledge and existence of uncertainties must be taken into account along with both existing alternatives and the potential for other new improved approaches. Receiving environments must be clearly defined and means to prevent spread to unauthorised environments must be identified.

There are reasons to be sceptical that self-limiting GMM will overcome the limitations of SIT (paragraph 1 p.xi) for mosquitoes and these should also be stated. A major disadvantage of GMM compared to SIT is the likely development of resistance, due to the reliance on a single genetic modification rather than multiple chromosome breaks.

It is unclear why the discussion has been led by "scientists involved in this research" (para 1, p.xi). This is not best practice and likely to be self-serving, particularly where a commercial company (Oxitec) is involved. A more inclusive process is needed, which does not exclude alternatives. See for example, Nuffield Council on Bioethics (2012) Emerging biotechnologies: ethical issues. On:

http://www.nuffieldbioethics.org/emerging-biotechnologies . Benedict and Alphey (refs cited) make a mistake that is repeated throughout the document. Whilst it is indeed correct that self-sustaining approaches may make it impossible to recall the GMM should anything go wrong, it is not correct to state that the effects of releasing self-limiting GMM can necessarily always be reversed by halting releases. Large-scale releases of self-limiting GMM are intended to have major effects on ecosystems and some potential adverse effects may not be reversible. Further, the self-limiting mechanism may be partial, ineffective or overcome by resistance over time. No justification is given for Luke Alphey of Oxitec's claim that only self-sustaining GMM require initial testing under physical confinement: he does of course have a strong vested interest in claiming this. Many issues, such as interactions between vector species (*Aedes aegypti* and *Aedes albopictus*), should have been tested by Oxitec prior to open releases of its GMM, but were not.

Who assesses efficacy (page xii)? Surely a regulator is needed?

COMMENTS ON KEY MESSAGES

Point 2, page xv: The sentence "Thus, the risk incurred by testing new and unproven strategies should be assessed against the risks to human health and the environment posed by maintaining the status quo, which includes both ongoing disease and exposure to broad spectrum insecticides" should be deleted, for the reasons argued above. Risk assessment does not include efficacy assessment and benefits should not be claimed by applicants before efficacy has been established. A separate chapter should have been included outlining who the customer is likely to be and how the risk assessment, efficacy assessment, alternatives, standards of care, and cost-effectiveness analysis might be combined to reach a decision at each stage. The alternatives to GMM include better implementation of existing strategies as well as the development of new non-GMM strategies. It is also incorrect to claim (in the absence of any evidence) that GMM will either prevent ongoing disease or reduce exposures to insecticides.

Point 6, page xv. The phrase "will decline" should be replaced by "is expected to decline". Add: However, mechanisms which could allow the genetic modification to persist will need to be tested as part of the risk assessment process. This sentence should be deleted: "In some cases, the GMM are meant to be sterile and thus unable to pass the genetic modification on to future generations through mating". Oxitec's GMM are not sterile and no sterile GMM appear to be proposed for release. Delete: "From a risk assessment perspective, these approaches can be reversed by halting releases and therefore are unlikely to produce permanent changes in the environment". This is not correct. Some potential adverse effects may not be reversible e.g. the establishment of a non-target vector due to reduced competition. Self-limiting approaches are intended to achieve significant changes in ecosystems, which are not guaranteed to be reversible. In contrast, replacement strategies are intended to leave ecosystems relatively unaltered by replacing existing disease vectors with a genetically modified version of the same species. In both cases, comprehensive risk assessments are needed.

Point 9, page xvi. This paragraph should reflect the fact that these advantages are theoretical (e.g. by replacing "can reach" with "may reach") and also list theoretical disadvantages. These include: the single-species approach may not be appropriate in areas where there is more than one disease vector or where a non-target disease vector may become established; complex interactions between multiple vectors, ecosystems and humans may make it difficult to predict the consequences of releasing GMM on human health and the environment; there is a high likelihood of development of resistance over time (potential for resistance developing via mutations is a major disadvantage for genetic self-limiting approaches compared to SIT); self-limiting approaches (SIT) have generally not been effective for mosquitoes partly due to complex density-dependent effects and GMM may not

overcome this and other problems; pathogens may evolve to become more virulent in response to reduced disease transmission properties. It is unclear why this paragraph mentions bed nets but not impregnated curtains, which have been tested for day-biting mosquitoes: Kroeger A, Lenhart A, Ochoa M, Villegas E, Levy M, Alexander N, McCall PJ (2006) Effective control of dengue vectors with curtains and water container covers treated with insecticide in Mexico and Venezuela: cluster randomised trials. British Medical Journal 332(7552):1247-52. This sentence is incorrect: "It is important also to note that GMM technologies are compatible with other disease control methods and could be incorporated into integrated vector management programs". Rather than noting that GMM technologies are compatible it is important to examine under what circumstances may or may not be compatible with other disease control methods and whether or not they can be incorporated into integrated vector management programs.

Point 10, page xvi. Phase 2 MUST involve testing under physical confinement: there is no excuse for omitting this step. Phase 3 may begin with testing under ecological confinement, as under geographic, spatial or climatic isolation, but other factors (e.g. whether the area is populated) also need to be considered: the requirements for proceeding to stage 3 should not be by-passed just because there is some form of ecological confinement. It should be recognised that no environment is fully isolated and GMM may be transported long distances by humans e.g. on clothing or in tyres. "Go/no-go" criteria must consider the extent to which existing the existing baseline and relevant processes have been established, identified and understood, in relation to disease vectors, ecosystems and disease transmission. Insufficient information and too many unknowns or too much uncertainty should be recognised criteria which could lead to a decision not to proceed to open releases (whether regarded as "ecologically confined" or not).

Point 15, page xvii. Independent verification of results should be REQUIRED. There should be some discussion of how this can be achieved. Does the WHO think efficacy should be regulated or not (as it is for other interventions such as vaccines)?

Point 19, page xvii. "Benefits" should be replaced by "efficacy" (benefits have not been established). It should be clear that this decision-making process is a separate process from risk assessment, which has well-defined core functions as outlined under point 20. Cost-benefit analyses require independent validation: Oxitec's cost-benefit analysis (on: http://www.plosone.org/article/info:doi/10.1371/journal.pone.0025384#s5) is extremely poor as it is based on unverified assumptions about efficacy and transmission thresholds and ignores any circumstances in which the releases might have a harmful effect (e.g. increase in other vector species, increase in DHF due to loss of cross-immunity to different serotypes). Not only the "risk" but the risk and benefits of alternatives must be considered. It should be recognised here that there will be significant unknowns and uncertainties in the decision-making process. The last sentence should be deleted. It is extremely confusing to define the term "causes more harm than current practice" as a comparator. What appears to be meant is that this should be the criteria on which releases should be allowed or not allowed, but, if so, this completely contradicts the rest of this paragraph and the entire report, which accepts that both risks and efficacy are relevant to the final decision and that a variety of factors may lead to go/no-go decision points. Both harms and benefits should be considered in the decision (as already noted) and alternatives; not all alternatives are mutually compatible or mutually exclusive. The term comparator has not been defined but often has a legal meaning (and is indeed given its usual meaning in point 23). For example, in the EU, Annex II of Directive 2001/18/EC specifies that "identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations". The non-modified organism from which the GM animal is derived is often termed the "conventional counterpart" and referred to as the comparator for the purpose of risk assessment. However, in the case of GMM

other comparators may also be needed: for example, mass releases of wild-type mosquitoes would clearly be unacceptable so mass releases of mosquitoes irradiated for use in the conventional Sterile Insect Technique (SIT) might be regarded as an additional comparator.

Point 20, page xviii. The concept of "receiving environment" needs to be introduced here. Receiving environments will have different characteristics such as: density of the target disease vector, presence or absence of non-target disease vectors, broader ecosystem characteristics and other species, presence or absence of humans and endemic or sporadic disease, characteristics of pathogens. Risks and benefits may vary considerably between environments and risk management measures may need to address whether and how it is possible to restrict releases to particular environments.

Point 21. It would be useful to add more detail regarding regulatory requirements here. For example, EU requirements are relevant because (i) Oxitec has proposed releasing GM *Aedes aegypti* in Madeira and may also consider releases of GM *Aedes albopictus* in Italy or elsewhere in the EU in future; (ii) transboundary notification requirements require Oxitec to supply a risk assessment which meets EU standards when it exports GMM eggs for open release in other countries (although the company has not correctly followed these requirements to date); (iii) the WHO/FNIH claim to be developing "best practice" which should take into account existing regulatory standards in developed countries. In the EU, conclusions required in the case of risk assessments for deliberate release of GMOs higher than plants (D.1) from Annex II of Directive 2001/18/EC are: 1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s). 2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s). 3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species. 4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable). 5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens. 6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s). 7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed. 8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s). 9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs.

Point 23. For self-limiting approaches, Phase 1 testing will also need to test conditionality i.e. the extent to which mechanisms developed to allow breeding to adulthood in the lab may allow inadvertent breeding to adulthood on release (e.g. by exposure to tetracycline in the environment, in the case of Oxitec's RIDL technology). Testing of GMM vector strains for disease transmission and insecticide resistance is also essential at this stage.

Point 24. The step "determination of the need for physically confined testing" should be omitted and replaced by a statement that physically confined testing is always needed. This may be a regulatory requirement in some countries. For example, in the EU 'step by step' principle in Directive 2001/18/EC requires containment to be reduced gradually step-by-step "only if the evaluation of earlier steps in terms of the protection of human health and the environment allows the next step to

be taken". Missing a step would not meet these regulatory requirements. Important information, e.g. on larval competition within and between vector species, needs to be collected at this stage. Ecosystem responses can be partially tested in caged trials and should aim to reduce uncertainties associated with open releases. It is confusing to list "physically confined" and "ecologically confined" testing as both part of phase 2. So-called "ecologically confined" testing would count as a deliberate or open release of GMOs and would normally trigger different regulatory requirements than contained use, including transboundary notification requirements. These differences should be clearly explained in the document. It is surprising that transboundary notification requirements are not discussed in detail in the report, particularly as Oxitec has so far failed to follow these correctly (as detailed in: http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf).

Point 25: Requirements for Phase 3 testing also apply to so-called "ecologically confined" testing (which is currently wrongly characterised as Phase 2 testing). Other important issues should be included in this list, such as impact of releases on other disease vectors; impact of releases on neighbouring areas (e.g. possible increases in target vector densities); potential for poor efficacy to impact negatively on health (e.g. through an increase in DHF due to loss of cross-immunity in dengue endemic areas) and potential for evolution of pathogens in response to the releases. It is surprising that whilst point 15 discusses the development of "go/no-go" criteria in the context of efficacy testing, there is no such discussion in the context of risk assessment and human and environmental safety issues. In particular, lack of knowledge, understanding or data regarding baseline disease vectors, ecology or disease transmission may be good grounds for not proceeding to phase 3. Just because something may not be measurable in phase 3 (e.g. development of resistance, pathogen evolution, human immune response, or ecological responses including potential increases in other disease vectors) does not mean that experiments should just press ahead and these issues be left to monitoring in phase 4. It may be necessary to devise further contained-use experiments and/or improve baseline study of ecosystems, pathogens or disease monitoring prior to allowing open releases, alongside better modelling, and perhaps halt the trials or chose a different receiving environment and/or alter the characteristics of the GMM proposed for release to improve biosafety. For example, in the UK, planned open releases of Oxitec's GM diamond back moths have been halted because Oxitec used a non-native strain, which might introduce new characteristics into the native DBM population. It is also unclear why monitoring is left to phase 4: in the EU a monitoring plan would be a regulatory requirement in phase 3. Similarly, cross-border issues will arise at phase 3 and should not be left to phase 4.

Point 26: Some discussion of the distinction between "experimental" and "commercial" releases in relevant countries would be helpful. In the EU, Directive 2001/18/C uses the term "placing on the market", where "placing on the market means making available to third parties, whether in return for payment or free of charge" (Article 2, paragraph (4)).

Point 27. It is unfortunate that Oxitec and Mosqguide encouraged Brazil to push ahead with open releases of GMM before specific regulatory guidance was agreed, as described in: Beech C, Quinlan MM, Capurro ML, Alphey LS, Mumford JD (2011) Update: Deployment of Innovative Genetic Vector Control Strategies including an update on the MosqGuide Project. Asia Pacific Journal of Molecular Biology & Biotechnology, 19(3), pp.101–106. This states: "*Brazil This country was used as an example in the original paper for the steps it had taken to consider specific applications of genetically modified insects within its existing regulatory framework for GMOs (Normative Resolution No7). The new regulation that covers GM insects (Normativa Insectos GM), and specifically GM mosquitoes which, as vectors of human disease, are classified at a higher biosafety level (NB2) than other insects, is still at the drafting stage at the time of writing. However, after presentation of a dossier, the*

National Biosafety Committee (CTNBio) took a decision in December 2010 on a specific case – to allow the open field release of male "genetically sterile" Aedes aegypti carrying RIDL® (OX513A, Phuc et al., 2007) traits at specific locations in the state of Bahia…"One hopes that the final sentence of this paragraph is an admission by the WHO that failure to wait for the development of specific regulations was a mistake. It would be helpful if the Mosqguide project report was published and some "lessons learned" were reported by the WHO.

Ethics and Engagement (pages xix to xxi): this chapter of the report is extremely poor and seems to consist largely of a weakly-argued post-hoc rationalisation for not seeking fully informed consent to Oxitec's trials of GMM to date. The argument (para 31) that Oxitec's failure to collect any data on disease incidence justifies not seeking consent is not consistent with the requirements of the Helsinki Declaration. In Brazil, the WHO-funded project Mosqguide appears to have assisted Oxitec in conducting a PR exercise which included the widespread use of a jingle which claimed the GMM were the "solution" to dengue fever (the jingle is reproduced in the LA Times here: http://articles.latimes.com/2012/nov/01/world/la-fg-brazil-mutant-mosquitoes-20121102) . It is completely unacceptable to claim that experimental releases provide a "solution" and Oxitec's partner researchers in Brazil have rightly been criticised by the regulators CTNBio for wrongly raising expectations for this experimental approach in this unethical manner. Point 33 appears to acknowledge that this is wrong, but does not admit that this error has already taken place or explain what remedial action might be taken. The lack of any "lessons learned" in the report allows this issue to be glossed over in a way that is completely unacceptable. There is also no discussion of transparency, consultation requirements and access to justice. At Oxitec's partners' request, the risk assessment submitted to CTNBio was withheld from publication, making it impossible for independent researchers or members of the public to comment on it or people affected by the trials to be fully informed. Best practice in terms of environmental justice is provided by the Aarhus Convention and it was this convention (implemented as part of the EU's transboundary notification requirements for the shipments of GMM eggs from the UK) which enabled GeneWatch UK to obtain copies of the (extremely poor quality) risk assessments for the Cayman Islands and Brazil (redacted) in the UK some months after the experiments had started (or, in the case of the Cayman Islands, been completed). In Malaysia a summary risk assessment was published and there was some public consultation, but the full risk assessment was withheld as commercially confidential. Failure to follow best practice in the countries where GMM have been released sets a poor standard and the Mosqguide project, riddled with conflicts-of-interest, is largely responsible for this. This report should begin with "lessons learned" by the project and not endorse poor practice. The pretence that no commercial interests are involved is a joke when Camilla Beech of Oxitec appears to have set most of the agenda for the project.

Regulatory Frameworks

Point 38. Efficacy is NOT regulated in the case of GMM (except in so far as poor efficacy may introduce risks which need to be considered in the risk assessment), so the first sentence in this paragraph is misleading.

Point 41. Again, the author appears to be unaware of the statement from Beech et al (2011), cited above and the fact that the Mosqguide project actively facilitated the bypassing of the development of GM insect regulations in Brazil. This is surprising. Is the WHO in favour of specific regulations and/or guidance being developed prior to releasing GMM or not? Is the WHO aware that Oxitec deliberately undertook its first releases of GMM in the Cayman Islands before the provisions of the Cartegena Protocol had been extended there and that Oxitec "forgot" to copy the risk assessment required by the transboundary notification process to either the EU or UK authorities (and that the company made the same error in the case of Brazil)? It is simply not correct to state that "human

health benefits are relevant as part of the regulatory decision-making process for GMM" (although human health risks are). Currently, only the GMO risk assessment is part of any regulatory assessment in any country: the role of risk assessment is clearly defined and does not include claimed benefits. There is no regulator for efficacy in the case of GMM (and the term "efficacy" not "benefits" should be used since efficacy has not yet been established, so any benefits are speculative). In the case of GM crops, decisions on cost-benefit have long been assumed to be left to the customer (i.e. the individual farmer) at a stage which follows regulatory approval. In the case of GMM, the customer may well be a national or regional government, which will indeed need information on risks, costs and benefits before taking a decision. However, regulatory frameworks for GMOs do not allow the weighing up of potential benefits, costs, alternatives etc. within the GM risk assessment (and this would anyway be extremely difficult as many alternatives may need to be considered). The Guidance Framework would benefit from a separate chapter on this decision-making process: it cannot be subsumed within the risk assessment as this paragraph and other parts of this report imply. It would also be useful (as noted above) if the authors would clarify who should conduct the independent efficacy assessment which is needed prior to a decision on implementation as a public health measure. The comment that authorities should "exercise discretion in imposing regulatory requirements" is based on a false assumption that there are no commercial interests in this field. In fact Oxitec has close links to multi-national company Syngenta which is seeking to establish a regulatory precedent for GM agricultural pests: the decision to focus on public health applications in the first instance is a key component of a PR exercise designed to weaken regulation. UK tax laws have been changed specifically to attempt to allow the company to work towards an IPO in the hope of obtaining substantial returns for its venture capital investors, which include Oxford University and a number of extremely rich individuals and investment funds.

Para 43. Regulatory process SHOULD include public consultation. It would be helpful if the WHO would state explicitly that Oxitec's practice of keeping risk assessments secret on the grounds of "commercial confidentiality" is unacceptable. Consultation is an ESSENTIAL part of ensuring that the risk assessment is as comprehensive and robust as possible. Further, people cannot give fully informed consent to trials if the risk assessment is not published as no one has any information to inform them with. Best practice is provided by the Aarhus Convention, which covers access to environmental information and environmental justice. It is surprising that this convention is not even mentioned in the report.

Para 44. Deliberate transboundary movement (i.e. shipping) should also be covered here e.g. notification requirements, publication requirements and the Biosafety Clearing House, need for emergency plans. Potential transboundary movement as the result of open releases should not be restricted to self-sustaining GMM: self-limiting GMM are not 100% effective and development of resistance or other failures could make transboundary movement an important issue. Mosquitoes have been transported worldwide via human movements.

Discussion of LIABILITY has been entirely omitted from this document – why?

COMMENTS ON INTRODUCTION

p.1 Summary: there are theoretical disadvantages as well as theoretical advantages: these should be acknowledged up-front e.g. limitations of the single-species approach where there are multiple vectors, difficulties predicting disease response. It should also be acknowledged that halting releases of self-limiting GMM may not prevent adverse effects from persisting (e.g. the establishment of another vector due to reduced competition).

p.1 First para. This seems rather thin on alternatives and references for dengue, where many experts argue that it is failure to implement existing measures, rather than a lack of available measures, which is the main problem. There is also important R&D in many areas other than GMM for dengue: e.g. impregnated curtains and water containers (see ref above on this); biological control, multiple new larvicides, vaccines (some refs are in the briefing on: http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf but there are many more).

p.2 3rd para: "either refractoriness or sterility" should be replaced by "either refactoriness or limited reproductive potential". It is unhelpful to refer to sterility since no sterile GMM are actually being proposed for release.

p.2 4th para. This para should recognise that this pathway may not be straightforward and limited efficacy, safety issues, or the need to make improvements in technology or to improve understanding of ecosystems or disease transmission could delay or halt the implementation of such programmes.

p.3 should note that "population suppression" is potentially more disruptive to ecosystems (since the aim is to significantly reduce numbers of the target population of mosquitoes), whereas "population replacement" raises greater concerns about the persistence of the GMM in the environment. However, impacts of both approaches need to be thoroughly assessed as part of the risk assessment process for open releases of GMOs. In the "self-limiting" section the following sentence is incorrect as it gives a misleading sense of certainty regarding the viability of progeny and does not acknowledge that late-acting lethality is not the same as sterility: "Indeed, a subset of the self-limiting approach is comprised of GMM that are sterile, or effectively sterile in that no viable adult progeny are produced from mating, and are thus unable to pass on the genetic modification to another generation". This paragraph should state instead: The "self-limiting" approach relies on releasing GMM which limit the number of viable adult progeny produced from mating and hence the amount of genetic material passed to future generations. The genetic modification may aim for "sterility" (in which case most of the released GMM do not reproduce) or late-acting lethality (in which case many of the GMM reproduce but most of their progeny do not survive to adulthood). The self-limiting modification is conditional in that a chemical switch is included to the GMM to survive to adulthood in the laboratory but not once they have been released into the wild.

p.3 final para. Should make clear that survival of offspring may depend on a number of factors which need to be tested e.g. conditionality, resistance mechanisms. The phrase "will be reduced" should be replaced by "is expected to be reduced if GMM males are released in sufficient numbers to mate with wild females".

p.4 Atkinson et al. (2007) contains many simplifying assumptions, as all models do. For example: it includes only one serotype of the dengue virus; only one vector species; a particular form for larval density dependence and other aspects of the mosquito life cycle, and for the disease transmission model; and (completely unrealistically) that the GM male mosquitoes compete just as well as wild ones. The mosquito population in the absence of control is unstable in this model and the model behaviour has not been validated by comparison with wild population behaviour, let alone compared to data obtained from Oxitec's GMM releases in the Cayman Islands or Brazil, which show that the mating success of the GMM mosquitoes is in reality very poor. Disease transmission assumptions also appear unrealistic as the model actually predicts eradication of the virus in the continued presence of the vector. Because the model includes only one serotype there are no cross-immunity effects, hence the risk of DHF cannot be calculated. This is important because partially effective vector reduction strategies in dengue-endemic areas can actually increase incidence of

DHF. See: Thammapalo S, Nagao Y, Sakamoto W, Saengtharatip S, Tsujitani M, Nakamura Y, Coleman PG, Davies C (2008) Relationship between Transmission Intensity and Incidence of Dengue Hemorrhagic Fever in Thailand. PLoS Neglected Tropical Diseases 2(7): e263. doi:10.1371/journal.pntd.0000263; and Nagao Y, Koelle K (2008) Decreases in dengue transmission may act to increase the incidence of dengue hemorrhagic fever. Proceedings of the National Academy of Sciences,105(6), 2238-2243. Further, because only one vector species is included in Atkinson et al. (2007) the possibility that disease transmission continues due to displacement of *Aedes aegypti* by *Aedes albopictus* also cannot be explored. It is not acceptable to treat the results of a single unvalidated modelling exercise conducted by Oxitec as if they somehow represent reality. This single paper certainly does not substantiate the claim that self-limiting approaches might substantially reduce vector-borne diseases! Its limitations should be admitted. Plus, it should be openly stated that it does not apply to malaria: it considers only a single vector-borne disease i.e. dengue. The claim that "effects could be withdrawn by halting releases" is also wrong (as noted above): some effects may continue even if releases cease.

p.4 This is a rather over-optimistic description of the current state of the "self-sustaining" approach, where many limitations have yet to be overcome. A lot more caveats should be included if the report is not to appear dishonest. The citation of Deredec *at al*., 2012, puts something of a positive spin on a paper which admits that it is not clear that the proposed mechanisms can be made to work and suggests that, if they do, 2-3 HEGs would be needed to target female fertility genes or a driving-Y chromosome would need to be transmitted to 75%-96% of progeny. The model also finds that eliminating the disease is not much easier than eliminating the vector, since *A. gambiae* is such an efficient vector. As above, this model contains many simplified assumptions about mosquito population dynamics and malaria epidemiology which may not be borne out in reality. Further, critical parameters used in the model (such as the maximum intrinsic growth rate of the mosquito population) are unknown. It is particularly important to note that this paper assumes only a single vector species, which is not the case in most of Africa. Impacts on human immunity are also omitted, although they may be extremely important in determining whether this strategy actually has any benefit to human health: see e.g. Scott TM, Takken W, Knols B.G.J, Boëte C (2002) The ecology of genetically modified mosquitoes. Science 298, 117-119. There is no discussion of the potential for pathogen evolution which may be particularly important in self-sustaining approach, as Medlock has suggested for dengue: Medlock J, Luz PM, Struchiner CJ, Galvani AP (2009) The Impact of Transgenic Mosquitoes on Dengue Virulence to Humans and Mosquitoes. The American Naturalist, 174, 565-577.

Table 1.1 The phrase "Will not persist" (for self-limiting, population suppression approaches) should be replaced with "Not intended to persist".

p.5 The disadvantages should be listed for both approaches, not just the advantages. These include: The single-species approach may not be suitable where multiple vectors co-exist or may become established as other vectors may persist or even increase in numbers; It may be difficult to predict the result of large-scale releases in complex ecosystems, including impacts on disease transmission; GMM approaches may lose efficacy over time due to the development of resistance; GMM approaches may require unacceptably high release ratios (of GM to wild mosquitoes) to suppress or replace wild populations; GMM releases may have poor efficacy due to density-dependence of mosquito populations; continued, repeated releases of GMM may be difficult to sustain or not be cost-effective; pathogens may evolve in response to reduced disease-transmission properties; it may be impossible to recall some GMM and adverse effects may not be reversible; use of GMM may not be compatible with some other interventions; partially or temporarily effect interventions may cause harm through complex effects on human immunity and disease (e.g. reduced cross immunity

to multiple dengue serotypes, leading to DHF, or reduced immunity leading to a rebound in cases of disease).

p.5-6 Potential utility of GMM. This is a one-sided description. Loss of immunity, as described in Ghani et al., 2009 is a likely consequence of GMM releases too, if they are effective at producing an initial reduction in disease transmission. Whilst it is true that GMM might be combined with vaccines this is also true of all other existing or proposed interventions. It is not at all clear that GMM releases are compatible with other strategies to reduce vector densities, since these will impact on the GMM mosquitoes perhaps before they have the desired effect of population-suppression or population-replacement. For example, spraying adults with insecticide during the releases will reduce the number of GMM males available to mate: they may be more affected by the spraying than the target females (which are acknowledged to be difficult to reach). In Oxitec's experiments in Malaysia, people were told that spraying would interfere with the results and in the Cayman Islands Oxitec chose a test site where there were no mosquito control measures. Predicting the combined effects of GMM releases and insecticides is likely to be complex, see e.g. for insecticides plus SIT: Thomé, R.C.A., Yang, H.M., Esteva, L. (2010). Optimal control of Aedes aegypti mosquitoes by the sterile insect technique and insecticide. Mathematical Biosciences 223, 12-23. Efficient removal of breeding sites also renders the GMM releases pointless and hence a waste of money. If release of GMM reduces compliance with traditional control measures such as removing breeding sites this could have adverse consequences. Claims about "disease eradication" are over-optimistic given current poor results. GMM approaches are likely to have limited benefits in areas where disease is not occurring. It is unlikely that GMM will be allowed to be released in areas where the modified species is not established as, even for self-limiting approaches, the existence of some surviving progeny plus the likely development of resistance over time means risking establishing a vector where it was previously absent.

p.6 Figure 1. Physically confined trials should precede ecologically confined trials: it is not an "and/or". This re-definition of "confined" is not compatible with regulatory requirements which make a clear distinction between deliberate open releases and contained use. Omission of physically confined (i.e. contained) trials is not compatible with the step-by-step approach.

p.7, para 2: Phase 2 MUST involve testing under physical confinement. This is an essential step for self-limiting as well as self-sustaining approaches. So-called "ecologically-confined" trials are not confined trials and will be regarded as open releases for regulatory purposes.

p.7, para 3: Characteristics of trial sites which need to be considered will include density of the target vector, presence of other vectors (or likely spread from neighbouring areas), presence/absence of humans, whether the target disease is present and endemic or not. Risks and benefits will vary according to the receiving environment and measures will need to be in place to prevent spread to unauthorised environments.

p.7 What is meant by "regulatory and other authorities"? There is currently no regulator for efficacy of GMM. Under current regulatory regimes, authorities may be involved in efficacy and cost-benefit analyses only in so far as they may be customers for the GMM.

p.8 1st para. Environmental safety MUST (not "may") be incorporated into long-term surveillance because GMO regulations will normally require a monitoring plan for all biosafety aspects.

p.8 2nd para. The recognition of the need for "go/no-go" criteria including efficacy and safety endpoints is welcome. But discussion of these should be included in the biosafety section of the report as well as the efficacy section.

p.8 Critical path for GMM development. 1st para in this section: risk analysis and cost-effectiveness analysis are two different steps in the decision-making process and should not be muddled up. Planning response in the case of resistance developing is important (and it is welcome that this is recognised here) but it is not at all obvious that it will be possible to develop "next-generation products" to address the problem of resistance when it arises. If this is not possible, then a rebound in disease cases is likely, including the possibility of an increased number of deaths compared to if there was no intervention in the first place. For this reason, resistance is not an issue to be parked at the monitoring stage, especially as evolution of resistance via mutations is not likely to occur in traditional SIT using irradiated insects (which have multiple chromosome breaks) and thus is an acknowledged downside to using genetic approaches to population-suppression compared to other alternatives (which might avoid this problem). Possible mechanisms and likely timescales for the development of resistance will need to be considered at an early stage and "go/no-go" criteria developed.

p.8 It is a bit of a myth that Oxitec is merely a small biotechnology company: the company has backing from Syngenta, the UK government and venture capitalists – including Oxford University - who expect to make a return on their investment (although it is unclear to what extent this is expected to arise from the commercialisation of GMM or of GM agricultural pests). All new technologies are risky in the sense that they often fail to perform as well as anticipated: hence subsidising further research and development of GMM has to be weighed up against investing in other R&D and/or spending more money implementing existing measures. It is always easy for researchers to argue that more money should go to them!

p.9 Figure 1.2 Column 1: "Modelling indicates utility" – a lot more is needed on this! It is always possible to write a model that indicates utility (and others that do not), what is needed is some discussion of the issue of model validation and also the need to develop alternative conceptual models so that important mechanisms are not missed entirely. The same problem applies to cost-effectiveness analysis: Oxitec has already done a cost-effectiveness analysis (as noted above) but it is clearly rubbish. There is some discussion of model validation in EFSA's draft GM animals guidance (which includes GM insects): http://www.efsa.europa.eu/en/consultationsclosed/call/120621.pdf ; and also in GeneWatch's response: http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/EFSA_GWresponse.pdf. Column 2: "appropriate regulatory bodies": biosafety is regulated for GMOs but efficacy is not (although poor efficacy may lead to some biosafety issues which need to be included in the risk assessment).

10) Do you have any specific questions on efficacy evaluation?

This is an important chapter: its presence is welcome and useful because until now other bodies (e.g. EU, Cartegena Protocol ad-Hoc Group) have looked only at the risk assessment aspects. However, apart from specific comments below it would be useful to know who is going to assess efficacy: currently there is no regulator for this (although risks due to poor efficacy will need to be considered as part of risk assessments which are normally a legal requirement under biosafety laws).

p.13 Last sentence: "reverse effects" is not correct: some effects may persist even if releases are halted (see comments above).

p.14 2nd para: It is unclear why applications for releases in non-endemic areas are excluded from the guidance. At minimum, the need to measure surrogate vector indicators and monitor health outcomes must be discussed. The word "powerful" should be deleted (who says it's powerful?).

Disease transmission is always a major consideration (even where disease is not endemic)! It is unlikely that mosquito control agencies in non-endemic areas would wish to consider releasing GMM unless they believed this would reduce the frequency of local transmission of sporadic disease or preclude the onset of transmission. Control agencies, public authorities and members of the public are likely to want evidence that this is likely to be achievable before implementing a programme of releases. It is important to avoid making unsubstantiated claims of health benefit where no evidence exists. Data will need to be collected to develop and validate models of mosquito populations and disease incidence in the relevant areas. Rather than excluding release of GMM in non-endemic areas from consideration, the Guidance Framework should consider what experimental evidence may be required to justify claims of benefit. When selecting release sites, Paragraph 17 of the Helsinki Declaration should be borne in mind "*Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research*" and Paragraph 20: "*Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects*": http://www.wma.net/en/30publications/10policies/b3/ . Monitoring of impacts of GMM releases on health and environment is also likely to be required as part of biosafety regulations (see Section 3).

Ethical requirements for trials should also be specified here. As specified in the Helsinki Declaration: "*The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins*". Contrary to the misleading claims made in the so-called ethics chapter of this report (which could perhaps be replaced by discussion of the relevant ethical issues in each section), fully informed consent is also required for all open release trials of GMM. See also: Macer D., 2005. Ethical, legal and social issues of genetically modifying insect vectors for public health. Insect Biochemistry and Molecular Biology 35, 649-660; Macer D (2003) Ethical, legal and social issues of genetically modified disease vectors in public health. WHO reference number: TDR/STR/SEB/ST/03.1. WHO reference number: TDR/STR/SEB/ST/03.1.

p.14. 4th para. This paragraph should mention the problem of cross-immunity to multiple dengue serotypes and DHF as described in Thammapalo et al. (2008) and Nagao & Koelle (2008) (cited above). Other issues that may impact on efficacy overtime are development of resistance and pathogen evolution e.g. Medlock et al. (2009) (cited above). Because they may give rise to harms to human health, immunity issues and pathogen evolution will need to be considered as part of biosafety assessments to meet regulations on open releases of GMOs. See e.g. the draft EU guidance on GM insect regulation developed by EFSA (cited above) – and consultation responses - and the draft CBD guidance on risk assessment of GMM (also cited above).

p.15 Validated computer models will need to be developed to describe the "baseline" vector and disease transmission behaviour in the site before release and to predict the possible outcomes of the experiments (including scenarios and uncertainty analysis). Development of vector and transmission models is an essential precursor to integrating data as described in the last paragraph on this page.

p.15 para 2. The purpose of any open release experiments should be clear and experimental protocols should be published in advance.

p.15, para 3. "will have different effects" should be replaced by "may have different effects" (this claim is based on unvalidated computer modelling).

p.15 Uncertainties, assumptions and unknowns in disease transmission models should be transparent and efforts should be made to explore alternative models and scenarios, explore parameter uncertainty, test assumptions, and validate model predictions at each stage.

p.16 para 3. It should be noted that trials in endemic areas may be riskier (due to possible adverse effects on disease transmission which will need to be considered in the biosafety assessment). On the other hand, trials in (especially populated) non-endemic areas may not provide sufficient potential benefit to justify the risks. For dengue trials, the presence or risk of DHF at the site will need to be considered due to the potential for a reduction in cross-immunity and an increase in DHF if vector suppression is only partially effective.

p. 16 last para. Many modelling exercises have predicted large fluctuations in mosquito densities as a result of releasing self-limiting GMM or irradiated sterile mosquitoes, including possible increases in mosquito numbers in areas surrounding the release site: e.g. Yakob L, Alphey L, Bonsall MB (2008) Aedes aegypti control: the concomitant role of competition, space and transgenic technologies. Journal of Applied Ecology 45, 1258-1265; White SM, Rohani P, Sait SM (2010) Modelling pulsed releases for sterile insect techniques: fitness costs of sterile and transgenic males and the effects on mosquito dynamics. Journal of Applied Ecology, 47(6), 1329–1339. A sufficient baseline must be established prior to releases at a site that any such increases could be identified. Otherwise it will be impossible to tell whether comparisons with neighbouring areas actually reflect (or partially reflect) increases in mosquito numbers in areas surrounding the release site. This is one of many problems with Oxitec's results from the Cayman Islands.

p.17 para 1. Limitations of markers should be tested and fully considered in design of trials (this is also important for biosafety monitoring) e.g. fluorescent markers may degrade with heat: Walters M, Morrison NI, Claus J, Tang G, Phillips CE, et al. (2012) Field Longevity of a Fluorescent Protein Marker in an Engineered Strain of the Pink Bollworm, Pectinophora gossypiella (Saunders). PLoS ONE 7(6): e38547. doi:10.1371/journal.pone.0038547.

p.17 para 3. It is far from clear that GMM will be compatible with conventional control measures. This should be thoroughly considered during the application for releases and is likely to be a requirement of the biosafety assessment (Section 3) as well as an ethical requirement. For example the CBD's draft GMM risk assessment guidance requires consideration of the effectiveness and availability of conventional methods of mosquito control (e.g., insecticides, larval site destruction, trapping) to control GMM strains as compared to the non-modified strain; and whether the release of GMM would affect pest control activities, such as the use of personal protection and insecticides that control other vectors. Even if e.g. response to insecticides is the same, spraying and removal of breeding sites may have a disproportionate effect on either the GMM or wild mosquitoes due to timing or location. For example, fogging during releases might kill large numbers of the male GMM before they mate with wild females but leave relatively inaccessible wild females unaffected. Implementation of best practice such as the efficient removal of breeding sites may render the release of GMM unnecessary and lead to GM males being unable to find GM females.

p.18 para 3. Impact on DHF also needs to be considered.

p.18 para 4. It is an over-simplification to state that regional dengue transmission is usually due to a single vector species as there are counter-examples in the literature (e.g. Paupy C et al. (2010) Comparative role of Aedes albopictus and Aedes aegypti in the emergence of Dengue and Chikungunya in central Africa. Vector Borne and Zoonotic Diseases (Larchmont, N.Y.), 10(3), 259–266) and in many cases the role of different vectors is unknown, or has changed from one species to another. One species may move into an area if another is reduced or eradicated (as Aedes albopictus

has done e.g. in China: Peng H-J, et al. (2012) A Local Outbreak of Dengue Caused by an Imported Case in Dongguan China. BMC Public Health 12, no. 1 (January 26, 2012): 83. doi:10.1186/1471-2458-12-83.). Further, low residual transmission by what previously may have been a secondary vector could prevent or reduce any impact of population suppression on disease transmission because transmission thresholds are low. It is difficult to understand why this paragraph states "it may be unnecessary to demonstrate epidemiological outcomes" and then goes on to explain a number of reasons why it IS necessary to demonstrate epidemiological outcomes. The last sentence of this paragraph should NOT be restricted to the case of vector population replacement, but should also include vector suppression strategies, which are equally novel and untested for mosquitoes. The comparator should not be "untreated controls" as ongoing disease control measures must be implemented as stated on page 17. Biosafety regulation will also require impact of human health risks due to issues such as human immunity effects and possible pathogen evolution (as noted in the draft guidance published by EFSA in the EU and in the draft CBD guidance).

p.19. The existence of multiple vectors in most areas is one of the disadvantages of the GMM approach, which is species-specific, and this problem may prove intractable.

p.20. 2nd para. Independent review should be required. What is the justification for omitting this? Access to environmental information, public consultation and access to environmental justice should meet best practice standards to ensure the best possible independent scrutiny (see comments on ethics and engagement chapter). The Aarhus Convention is relevant to this.

p. 20 3rd para. It is puzzling why the discussion of surrogate endpoints is not extended to non-endemic areas which are (for no obvious reason) excluded from this part of the guidance framework in comments on p. 14.

p.20 4th para. Models should be validated before open trials, in the first instance, so that the relevant parameters are based on measured values at the site and the ability of the model to reproduce the undisturbed system is known. Some data will need to be collected from laboratory work and caged trials, but field data will also be needed. The importance of collecting field data from the site e.g. on mosquito species, disease transmission, larval competition and density-dependent effects has been omitted from the Guidance Framework. Further validation will of course be needed at each stage to ensure that models continue to represent the disturbed system well enough to inform go/no-go policy and regulatory decisions. It would be helpful to cite some literature on model validation since this term is often misunderstood. See e.g. Rykiel Jr. EJ (1996) Testing Ecological Models: The Meaning of Validation. Ecological Modelling 90, no. 3 (November 1, 1996): 229–244. doi:10.1016/0304-3800(95)00152-2. It is important to consider conceptual validity as well as data/parameter validity as this is often a major source of error. If relevant concepts are not included, data will not be correctly interpreted and surprises will occur, potentially including harm to health or lack of efficacy. An example is the issue of cross-immunity to DHF: if this mechanism is not included in the model when GMM releases are made in high-transmission dengue-endemic areas then harm due to loss of cross-immunity will not be predicted. Similarly, if only one vector species is included in a model, continued disease transmission by another species will not be predicted. There is much relevant literature in other areas of environmental modelling e.g. Bevan K (2002) Towards a coherent philosophy for modelling the environment. Proc. R. Soc. Lond. A, 458, 1–20.

p.20 5th para. Models should be sufficiently well developed and validated to be able to reproduce annual and seasonal variations in vector abundance and distribution and disease transmission in the absence of GMM releases before any open release trials are contemplated.

p.21 2nd para. “sterile-male” should be replaced by “reduced fertility male”. The citation of Yakob and Bonsall (2009) should say MAY perform differently, not WILL perform differently, as this is an unvalidated model.

p.21 3rd para. This paragraph should mention potential problems caused by multiple vectors, difficulties establishing a disease transmission threshold for dengue, and the issue of loss of cross-immunity to multiple dengue serotypes which could increase incidence of DHF if population suppression is partial. Possible long-term impacts of loss of efficacy (e.g. through the development of resistance) or pathogen evolution should also be discussed.

p.21 Characteristics of the strain which need to be tested include insecticide resistance and disease transmission properties. Release of non-native strains should be avoided.

p.22 2nd para. Resistance may spread quickly and every effort should be made to predict possible mechanisms and timescales and to test these in laboratory settings before a commitment is made to a GMM release programme. Conditionality should also be tested as self-limiting approaches normally include a mechanism through which the insects can be bred in the lab e.g. in the presence of tetracycline. Dose-response curves of survival to adulthood in the presence of tetracycline should be published and surveys of tetracycline presence in the proposed release environment should be conducted (including e.g. measurement of levels in discarded take-aways in urban environments, and in septic tanks where mosquitoes may breed).

p.22 Final para. Release ratios (of GMM to wild-type) are one useful measure of efficacy and should always be reported. A useful comparator for the efficacy of self-limiting GMM approaches is the Sterile Insect Technique (SIT) using irradiated insects. However, the comparison with Medfly is misleading because SIT has been much more successful for Medfly than mosquitoes for a variety of reasons including larval density-dependence in mosquito populations. Self-limiting GMM have a number of disadvantages compared to SIT, including the likely development of resistance and the existence of a number of characteristics and mechanisms (conditionality, late-acting lethality) which may introduce biosafety risks. Important information for decision-makers may therefore include the performance of GMM relative to SIT (both efficacy and risks).

p.23 Top line. Delete “In contrast”.

p.23 Header “Independent verification of results should be considered” should be replaced with “Independent verification of results is required”. Next para: Why should the research team establish the “independent monitoring body” (which will then not be independent, and not perceived to be so)? Final para: A DSMB IS needed for trials which do not include epidemiological outcomes.

p.24 1st para. To be free of “conflicts of interest” a procedure is needed to declare, publish and check these, and the research team should not set up its own monitoring body! A similar procedure might have been helpful in the preparation of this guidance and much other guidance worldwide: http://www.genewatch.org/article.shtml?als[cid]=567356&als[itemid]=571485 .

“Go” and “no-go” criteria are important but should also relate to biosafety issues (not just efficacy)

p.24 4th para: “can be linked” should be replaced by “may be linked” as the precautionary principle is a legal requirement. More discussion of uncertainties is needed here. Lack of understanding and information (e.g. inability to validate models and describe relevant ecological or disease transmission processes sufficiently well) is also a ground for not proceeding (which is often lacking, as admitted on page 47). For example, in the EU, Directive 2001/18/EC which covers the deliberate

release of GMOs says: "*The precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it*". It also says: "*The introduction of GMOs into the environment should be carried out according to the step by step principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step,* ***but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken***". In terms of efficacy (as opposed to biosafety) the ethical principles in the Helsinki Declaration are important as lack of efficacy in comparison to alternative approaches, or indications that benefits do not outweigh risks, are also reasons to discontinue trials. Reference should be made to Articles 6, 13, 17 and 20: http://www.wma.net/en/30publications/10policies/b3/ . Regarding remediation it should be acknowledged that some adverse impacts may not be able to be remediated (costs and liability are also relevant and this issue should be included in this document somewhere).

p.24. The Helsinki Declaration is also relevant here, as donors, researchers and public authorities must follow ethical principles. This is particularly important in the case of an "initial failure": participants must also be fully informed about such failures as they may wish to withdraw consent before donors or public authorities do. The view of an independent ethics committee on whether benefits continue to outweigh risks is also needed as the developer's "persuasive case" may not be entirely disinterested (especially if they have a commercial interest in getting a GMM product to market). Failure to halt trials when necessary could harm future research programmes conducted by the same research team or others (perhaps with improved knowledge or technology) as there may be a loss of public trust.

p.25. 1st and 2nd paras. Monitoring of epidemiological outcomes during open release trials is likely to be essential for biosafety purposes as a monitoring plan is normally a regulatory requirement for deliberate open releases (including in so-called "ecologically confined" trials which are here wrongly categorised as phase2).

p.25. Phase 1. Laboratory population studies. 4th bullet point, delete "when the strain is refactory": all strains should be tested for disease transmission properties. Missing bullet points: Multi-generational stability (for the anticipated duration of the open release programme); Resistance mechanisms; Tests of conditionality for conditional lethal approaches; pathogen evolution. Methods to validate model predictions also need to be developed at this stage.

p.26 1st para: NO, NO, NO: both types of trials ARE necessary: it is not acceptable to skip caged trials. For trials in physical confinement, missing bullet points are: interactions with other species, including competitors, prey, hosts, symbionts, predators, parasites and pathogens; resistance mechanisms e.g. changes in mating preferences of wild females over time. See: Hibino Y, Iwahashi O, 1991. Appearance of wild females unreceptive to sterilized males on Okinawa Is. in the eradication program of the melon fly, Dacus cucurbitae Coquillet (Diptera: Tephritidae). Applied Entomology and Zoology, 26(2), 265–270. So-called "ecologically confined" trials should be part of phase 3. Model validation, not just refinement, is required. Release ratios should always be published. For populations suppression approaches, a comparison with the traditional (non-GM) SIT should be made.

p.27 top bullet point: The word "sterility" should not be used to describe GMM, it is misleading. 2nd bullet point: delete "for refractory GMM" and add a requirement to assess changes in disease transmission properties over time.

p. 27 Phase 3. Before phase 3 it is ESSENTIAL to obtain prior baseline surveys of all relevant vector species including e.g. vector adult and larval densities and their seasonal and longer-term variations,

disease transmission properties, dengue serotypes, EIR, human antibodies and disease incidence etc. Release ratios must be reported for population suppression strategies. Compatibility with other mosquito control measures must be tested. Model validation is required (not just "refinement"). Pathogen function and mutation must also be monitored and the potential for the pathogen to evolve in response to the GMM releases must be fully considered. Disease incidence/prevalence studies require established baselines.

p.28 Bullet points: "passive case detection" (last bullet point) may be insufficient: monitoring must be powered to detect any problems promptly. Not only the target vector but also other vectors will need to be monitored (inside and outside the target area) as they may increase their role in disease transmission as a result of the GMM releases (or perhaps for other reasons). Vectors and pathogens must be monitored for development of resistance or increased virulence etc.

p.28/29 Capacity Building. Capacity building is expensive and costs of capacity building, monitoring etc. must be considered up-front as part of the decision-making process. Development of GMM require significant up-front investment and venture capital investors will wish to obtain a return on their investments. Any public subsidy of this process needs to be carefully considered and publicly justified.

11) Do you have any specific questions on biosafety?

Export/import and transboundary issues have been entirely omitted from this chapter. Shipments of GM mosquito eggs by Oxitec from the UK have to date failed to follow the correct procedure, which requires a risk assessment which meets EU standards to be made publicly available.

p.33 Summary. This chapter attempts to redefine regulatory biosafety requirements: the purpose of risk assessment is to assess risks not claimed benefits, hence the first sentence of the summary is incorrect. As stated on the following page, loss of efficacy is only relevant to biosafety in so far as it gives rise to risks (which, in some cases, it may). Beyond this, assessment of efficacy (a prerequisite to establishing any benefit and hence to weigh up the pros and cons against the status quo or other options) is NOT part of risk assessment. It is not clear how any concerns at all are to be raised let alone "evidence that a concern is valid" be sought or provided, given that to date trials have gone ahead in 3 countries without published risk assessments. This requirement in any case is contrary to the precautionary principle which is an international requirement and a legal requirement in many countries. There is much use of the term "acceptable" risks without any reference of how acceptability is to be determined: in particular requirements for access to environmental information and access to justice (e.g. the Aarhus Convention) are entirely omitted. Much of the Chapter reads like a description of what Oxitec would like the requirements to be, rather than what they actually are. This is not surprising given that its lead author is employed by one of Oxitec's investors and is receiving UK government funds to assist Oxitec to develop regulatory processes which suit its own commercial interests. The credibility of the Chapter is further undermined by the fact that in practice Oxitec has not met the necessary standards. See: Oxitec's Genetically Modified Mosquitoes: Ongoing Concerns. GeneWatch UK. August 2012. http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf

2nd para of summary: the concept of "exposure" (borrowed from toxicology) is not very helpful for risks which are not based on a simple dose-response relationship. GMM work indirectly to (attempt to) reduce disease incidence/impacts via complex ecosystem responses (intended to lead to reduced disease transmission). Unlike e.g. the level of exposure of a pesticide, many risks arise from complex interactive effects e.g. on human immunity, competitor species and vector or pathogen evolution.

3rd para: physically AND ecologically confined trials are both required (see above). Effects on human and animal health need to be mentioned in this paragraph.

4th para of summary. This definition of how to "achieve biosafety" is incorrect. The overall risk assessment endpoint is NOT whether GMM implementation causes more harm than current practice (which is in any case impossible to determine). This contradicts other parts of this document which accepts that the decision making process will include consideration of efficacy, cost-effectiveness, alternatives etc. Further, it misinterprets what a risk assessment is. The EU requirements for risk assessments for deliberate open release of GMOs other than plants have been cited above: these should be cited here rather than just making something up.

p.34 First para: There is a deliberate confusion here between "confined" and "contained" which conflicts with regulatory definitions. The best way to avoid this would to remove the so-called "ecologically confined" trial phase from phase 2 and include in phase 3, as noted above. From a regulatory biosafety point of view open trials are open trials! Rather than citing the EFSA draft guidance (which is poor and partly written by the same author) the actual EU regulatory requirements in Directive 2001/18/EC should be cited.

p.34 2nd para. 1st bullet point, add "or worsen health impacts". This can happen e.g. via immunity or cross-immunity effects without transmission being increased.

p.34 Final para: Should acknowledge that no specific guidance on GMMs has yet been adopted anywhere in the world, although draft guidance has been published by the CBD and the European Food Safety Agency (EFSA). The author does not seem to understand the precautionary principle or the need to address uncertainties and absence of evidence: the onus is on the applicant to justify the proposed release, not on others to demonstrate hazards. Further, an open and transparent process of consultation and relevant access to justice requirements are essential to ensure relevant issues are included and addressed.

p.35 The 2nd para is muddled. Last sentence "decisions would also consider benefits and costs" is not correct in the context of the risk assessment itself, which is a separate regulatory requirement. For example, in the EU, EFSA's Guidance on the environmental risk assessment of genetically modified plants states clearly: "*The overall risk/benefit is out of the remit of the EFSA mandate. The ERA should primarily focus on potential environmental risks arising from the GM plants*". See: EFSA Journal 2010;8(11):1879. This confusion is continued into the 3rd para which talks about setting against the risks of "no action". This is frankly, rubbish, and contradicts other parts of the report. The ultimate decision-making by the "customer" will consider efficacy (i.e. the extent to which claimed benefits might be delivered), cost-effectiveness and alternatives (both existing and emerging). But this is not part of the risk assessment and cannot be made to be so for legal reasons (i.e. because it's an attempt to redefine what risk assessment is) and for practical reasons (i.e. because benefits are not established and there will be many competing claims for alternative approaches). It is misleading to claim the concept of "causes more harm" has been used in Australia - this has not been used for GMM releases, but has been used by scientists conducting wolbachia releases. These are not GMM and thus not subject to regulatory requirements for GMOs and the merits of their approach have not been discussed extensively by members states and observers etc. It is bizarre to make up new regulatory requirements for GMOs in the pages of what claims to be a guidance framework!

p.35 3rd para. The idea that risk communication is an important part of public engagement would have more credibility if Oxitec's risk assessments had actually been published and consulted on!

Mosqguide did not communicate risks but claimed a “solution” in a jingle in Brazil. Some “lessons learned” would therefore be useful in this section.

p.35. Last para. Why are the EU risk assessment requirements for GMOs other than plants not cited here? To repeat: In the EU, conclusions required in the case of risk assessments for deliberate release of GMOs higher than plants (D.1) from Annex II of Directive 2001/18/EC are: 1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s). 2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s). 3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species. 4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable). 5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens. 6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s). 7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed. 8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s). 9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs.

p.36 1st para. Should acknowledge that no standard procedure has yet been established for risk assessment of GMM in any country. This para should not refer to potential benefits (which are part of the efficacy chapter not the biosafety chapter) but to potential HARMS. There is considerable additional complexity in assessing releases of large numbers of GMMs as this is a step beyond the relatively simple scenario of replacing a field of non-GM plants with GM plants. GMM are highly mobile and deliver their intended and unintended effects via complex interactions with a system consisting of multiple vectors, pathogens, humans and other species. This complexity should not be downplayed or the report will lack credibility.

p.37 2nd para: An explanation is needed for “the effects are not specified as harmful in regulations”: it is not clear what this means. Last sentence should say “can SOMETIMES be reduced to acceptable levels”: this is not always the case and claiming that it is contradicts the “go/no-go” approach described earlier. It would be helpful if the author could conceive of any circumstances in which proposed releases of GMMs might not be approved.

p.37. It is incorrect to state that the evaluation of risk “should be set against the benefit” – this is NOT part of risk assessment. Efficacy must be assessed separately and considered alongside other factors (including alternatives) when making a decision. The report would benefit from a separate section on the decision-making process, rather than a muddled and misleading attempt to subsume it under biosafety.

p.38 First para. The concept of using mosquitoes sterilised through irradiation (SIT) as a comparator should be considered in the efficacy section also.

p.38 3rd para. Issues include the disease transmission properties of the introduced strain and insecticide resistance properties.

p.38 The statement that "the RA should be associated primarily with the genetic modification" is incorrect: this is only one aspect. In the EU Annex II of Directive 2001/18/EC, part B states that "*identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations*". However, unmodified mosquitoes would not be released in millions in the kind of programme envisaged for GMM i.e. there is no corresponding use. If this is not considered, any GMM could be released in large numbers provided it was deemed less dangerous than releasing large numbers of unmodified mosquitoes. But this would be nonsense and is not what the regulation requires. According to the Directive: "*Depending on the case the e.r.a. has to take into account the relevant technical and scientific details regarding characteristics of: the recipient or parental organism(s); the genetic modification(s), be it inclusion or deletion of genetic material, and relevant information on the vector and the donor; the GMO; the intended release or use including its scale; the potential receiving environment; and the interaction between these*". The genetic modification itself is therefore only part of the assessment: the intended releases and their interactions with the receiving environment are also part of the assessment.

p.39 1st para. The conditionality of any lethality effect also needs to be tested.

p.39 2nd para. Markers should be tested e.g. fluorescent markers may degrade with heat.

p.39 last para. The need for longitudinal caged trials should be reflected in the definition of phase 2 tests elsewhere in the report: i.e. caged trials are ALWAYS required to produce this data. Interactions with other species (e.g. larval competition between vectors) should also be studied in caged trials. The need for field ecological studies to establish the baseline ecology and disease transmission (as discussed further on p.47) should be included as an additional phase BEFORE open trials (i.e. before phase 3 and also before so-called "ecologically confined" trials, which are currently wrongly included in phase 2).

p.41 1st para. It is incorrect to state that nuisance biting should not pose a hazard as large numbers of female biting GM mosquitoes may be released due to imperfect sorting mechanisms, or may survive in future generations (Reeves et al. 2012). It is also possible that mosquito densities increase in surrounding areas as a result of GMM releases. In addition, GM mosquitoes may be ingested in large numbers as releases of male GM mosquitoes must significantly outnumber wild populations, especially for population suppression. In the Cayman Islands, Oxitec's experiments resulted in complaints about mosquito numbers: see supplementary material in Harris et al (2012). In Brazil, the LA Times reports that it is impossible not to swallow some of the GM mosquitoes used in Oxitec's experiments: http://articles.latimes.com/2012/nov/01/world/la-fg-brazil-mutant-mosquitoes-20121102 . It is not for the Guidance Framework to prejudge whether new proteins expressed by GMM will or will not pose a hazard via allergic reactions or other mechanisms: this should be tested as part of the risk assessment.

p.41 2nd para. Should recognise that release of females will pose hazards due to potential to transmit disease as well as possible allergic reactions due to biting. Also, reduced efficacy can give rise to harms such as a rebound in disease cases or loss of cross-immunity to multiple dengue serotypes.

p.41 3rd para. An explicit phase 2b or similar should be included for collection of baseline data.

p.41 final para. Tests of potential hazards during the production process should be published before moving to the next stage, including tests of stability, conditionality, resistance. This data should be

incorporated in a risk assessment for publication and consultation meeting best practice standards consistent with the Aarhus Convention.

p.42 Mathematical modelling subsection. It is important to discuss requirements for model validation and development of alternative conceptual models, as noted above. See e.g. Rykiel Jr. EJ (1996) Testing Ecological Models: The Meaning of Validation. Ecological Modelling 90, no. 3 (November 1, 1996): 229–244. doi:10.1016/0304-3800(95)00152-2. There is some discussion of model validation in EFSA's draft GM animals guidance (which includes GM insects): http://www.efsa.europa.eu/en/consultationsclosed/call/120621.pdf ;
and also in GeneWatch's response:
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/EFSA_GWresponse.pdf.

p.42 Penultimate para. The term "sterile" should not be used. The term "level of exposure" is difficult to define for GMM trials as many hazards are not directly dose related (unlike e.g. toxicological hazards). Many GMM intended and unintended effects on the main endpoint (disease) occur via complex ecosystem interactions and, as noted on p.43, changes to target vector populations (and – although not mentioned – non-target vector populations)may have a detrimental impact on the wider environment and/or human health. Whilst it is true that contained use trials limit exposure (except if there are escapes), risks of open release trials are not necessarily less for population suppression approaches and the term "exposure" is rather meaningless.

p.43 1st para (Risk assessment). Should acknowledge that changes in non-target vector populations or other species (not just target vector populations) may also have detrimental impacts.

p.43 3rd para. Physically confined trials (caged trials) will always be needed because additional information e.g. on ecosystem interactions will be needed prior to open releases. For example, for population suppression approaches this might include larval competition studies between target and non-target vectors. It is likely that caged trials will be a regulatory requirement in many countries (e.g. in the EU, a phased approach to testing is required under Directive 2001/18). Results of phase 1 testing might also lead to a decision to abandon a particular technology or refine it (e.g. conduct further molecular biology work to improve penetrance or stability of the trait). This section should include discussion of go/no-go criteria as introduced in previous chapters.

p.43 Phase 2 heading and last para – So-called "ecologically confined" field trials should not be included in this section as they are really open trials and regulatory requirements for open trials will apply. Further, depending on what is proposed, other factors, such as whether an area is populated, presence of non-target vectors, presence of multiple pathogens or serotypes, immunity of population etc. may be more relevant to risk assessment and management than geographical features. This whole section is very confusing for the reader due to the muddling of open release and contained trials (which have different regulatory requirements).

p.44 1st para. It is unclear why this para says that Phase 3 trials are likely to be conducted in a location where the target disease is endemic. This is not correct. So far, Oxitec has conducted open trials in a non-endemic area on Grand Cayman, a sparsely populated area in Malaysia, an endemic populated area in Brazil and has proposed trials in Florida (a non-endemic populated area). Caged trials of a different GMM product have also been conducted in Mexico and a wide variety of other sites have been proposed e.g. in Panama, Madeira. Proposed sites for phase 3 trials are therefore likely to have varied characteristics including: populated or not and in varied ways e.g. villages or suburbs; endemic disease or not; local population immunity or not and extent of non-immune immigration (including e.g. non-immune armed forces); multiple or single vectors for target disease; for dengue, multiple or single serotypes and presence/absence of DHF; presence or absence of other

vector-transmitted diseases; varied ecosystems and living conditions (e.g. presence/absence of piped water and sewage systems, types of mosquito breeding sites available); different ecosystems. Because presence of people introduces additional risks, a staged approach requires that open trials should be conducted first in unpopulated sites with strict measures to seek to prevent spread of GMM to other areas. For vectors that are sufficiently promising in phase 2 (passing the go/no-go) tests, it is possible that impacts on target and non-target vectors (entomological endpoints) could be studied in this way if suitable sites can be identified and appropriate risk management measures can be devised. However, caged trials in such areas should always be conducted BEFORE open trials, to establish as much data as possible on risks e.g. due to ecosystem interactions (e.g. larval competition) and entomological efficacy prior to a go/no-go decision on open releases. When considering open releases, ethical requirements (Helsinki Declaration) must be taken into account as discussed below. Trials which are unlikely to benefit the exposed population (due to expected poor efficacy) should not be conducted. Areas surrounded by deserts, mountains or water may be POPULATED! Also, mosquitoes (including GMM mosquitoes) and disease are transported in and out of such areas via human movement, which has been a major factor in spread of mosquito vectors worldwide. The concept of "ecologically confined" trials should NOT be included in phase 2 but may be useful in phase 3 as part of a phased approach: however, it should then be considered in combination with other measures as a way to limit risks during study of entomological endpoints e.g. by choosing an ecologically confined UNPOPULATED area and implementing strict risk management (e.g. limit access to the research teams, fumigate ships etc.). Establishment of baseline (as discussed on p.47) is also essential before any open releases, including so-called "ecologically-confined" trials.

2nd para. Why is there no discussion of vertical gene transfer here? In general discussion of risks is very thin. See for comparison, EFSA's draft GM animals guidance (which includes GM insects): http://www.efsa.europa.eu/en/consultationsclosed/call/120621.pdf ;
and GeneWatch's response:
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/EFSA_GWresponse.pdf
and also the CBD draft guidance (pages 43-51): http://www.cbd.int/doc/meetings/bs/mop-06/official/mop-06-13-add1-en.pdf
Why is only a single ref given for HGT? The conclusion that HGT from GMMs "may be expected to be even rarer" than from GM plants to microorganisms appears speculative. There is actually a major gap in knowledge on this subject. See e.g. Silva JC, Loreto EL and Clark JB (2004). Factors that affect the horizontal transfer of transposable elements. Curr. Issues Mol. Biol. 6, 57-72. HGT has recently been observed between fish and lampreys: Kuraku S, Qiu H and Meyer A. (2012). Horizontal transfer of Tc1 elements between teleost fishes and their vertebrate parasites, lampreys. Genome Biology and Evolution doi:10.1093/gbe/evs069. There appears to be very limited knowledge about HGT between mosquitoes and other organisms. The purpose of Guidance should not be to dismiss potential hazards but to ensure that they are thoroughly investigated.

p.44 last para. Should say MAY lead to more effective suppression. The idea that late-acting lethality may improve population suppression due to larval competition is based on unvalidated computer modelling. Phase 2 trials must provide information necessary to evaluate risks as well as efficacy. A step by step approach requires that "the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken" (Directive EC 2001/18).

p.45 This paragraph should be deleted: it reads as a weak and unacceptable justification for Oxitec's failure to conduct caged trials. Caged (physically contained) trials are an essential of the step-by-step approach which is a legal requirement in the EU under Directive EC 2001/18. Important aspects of the RA require data that must be collected from contained experiments prior to open release e.g.

information on larval competition and interactions with "*competitors, prey, hosts, symbionts, predators, parasites and pathogens*". Since poor efficacy can also lead to risks (e.g. due to partial or temporary population suppression) and a reasonable expectation of efficacy is also an ethical requirement to conducting medical research (Helsinki Declaration), efficacy must also be tested as far as is possible in caged trials prior to any open release.

p.45 2nd para. This should all apply to contained (caged) trials. Studies must include impacts on competitor species, especially other vector species due to the potential for these species to play an increased role in disease transmission as a result of releases of GMMs. Studies of stability of the transgene must be of sufficient duration to cover the period of expected open releases and beyond.

p.45 Last para. Transport risks (e.g. during shipment of GM mosquito eggs to relevant countries) should also be included.

p.46 Phase 3. All these requirements also apply to so-called "ecologically-confined" releases which are really open releases of GMOs.

p.46 1st para. Disease transmission properties should first have been tested under contained use (phase 1 and 2). Phase 3 will also study efficacy (as outlined in previous chapter) but efficacy is also relevant to risk assessment in so far as poor efficacy may give rise to risks. It is essential to establish baseline ecology and disease burden PRIOR to phase 3 and this should ideally should have been included as a separate phase.

p.46 2nd para. Whether an area is populated and whether there is endemic disease etc. are also important considerations (see phase 2 above). It is not clear what "isolated" means: does this term include populated areas? Presence of multiple vectors is also an important consideration.

p.46 final para. It is unclear why no non-target organism effects are included here (especially effects on non-target vectors, which have potential to increase disease burden e.g. if population suppression of the target vector results in reduced competition).

p.47 1st para. Final sentence should also refer to non-target vectors (which can also increase the entomological or epidemiological burden).

p.47 2nd and 3rd paras. These are very important: a separate phase should be included PRIOR to open releases to incorporate the studies necessary to establish ecological, entomological and disease transmission baselines (including human immunity) and to validate models of mosquito population dynamics and disease transmission in the absence of GMM releases. Other vectors MUST also be included in the baseline studies and model validation, including interactions with the target species. In the absence of such studies it will be impossible to assess risks of increases in competitor species prior to GMM releases. Inadequate knowledge or understanding of the baseline must be recognised criteria to prevent or halt open trials.

p.47 Risk management. It should be recognised that stopping releases may not reverse all potential adverse effects (e.g. establishment of a new competitor species, evolution of a pathogen to become more virulent). Go/No-go criteria must therefore exist to prevent open release or halt a planned set of experiments completely if necessary.

p.47 final para. Implications of loss of efficacy for biosafety must be understood PRIOR to releases i.e. this is NOT just a monitoring issue. For example, loss of efficacy might lead to a rebound in cases of disease due to lowered immunity if a programme is initially successful. Poor efficacy can also lead

increase in DHF due to loss of cross-immunity to different dengue serotypes due to partial population suppression (see above). Thus mechanisms for loss of efficacy and timescales over which it might occur should be predicted based on modelling and data PRIOR to any open releases, and the consequences (especially for health) should also be predicted. These predictions may lead to a decision not to proceed to open release trials, or to a decision to proceed in a step-by-step approach. The next step from contained trials should be trials in unpopulated areas because this should allow validation of the entomological part of the model prior to exposing human subjects to unnecessary risks. All trials in populated areas should REQUIRE disease monitoring because of the potential for unintended effects (including outside the release area). In order to be consistent with a step-by-step approach, trials in populated areas should only take place only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken (Directive 2001/18/EC). Ethical requirements (the Helsinki Declaration) also require results of efficacy studies to be considered as there must be a reasonable likelihood that populations in the area of experimental releases will benefit.

p.48 Regular sampling should be REQUIRED, not merely considered.

p.48 para 2. It is difficult to understand why the "potential for evolution and adaptive processes" is not considered until phase 4! This will be a requirement in the risk assessment PRIOR to any open release (see the EFSA and CBD draft guidance documents). As explained above, risks associated with loss of efficacy are not purely a risk management issue: these are risks which could lead to serious adverse health effects and which may lead to a decision not to proceed to phase 3 (based on modelling and data collected in earlier phases). Unexpected loss of efficacy could also lead to termination of phase 3.

p.48 final para should be deleted. This is speculative and does not include potential risks that must be assessed, including possible establishment or increases in other vector species. Further, the "removal" of a vector is not anticipated in any realistic proposal to date (population suppression approaches are expected to require repeated ongoing releases to reduce the target vector population). It is also frankly bizarre that non-target species effects are left until the post-implementation phase.

p.48 Final sentence. Corporate bias and conflicts-of-interest must also be avoided.

p.49 1st para. Again: why are non-target organisms (NTO) left until the post-implementation phase? Draft EU and CBD requirements would require NTOs to be considered from the start and certainly to be included in the risk assessment PRIOR to any open releases, not merely once commercial releases are taking place (!!!). Did Oxitec write all of this chapter? Truly awful.

p.49 Risk management. 1st para: the phrase "would benefit from the availability of appropriate baselines" should be replaced by "REQUIRE appropriate baselines". This is not merely ESSENTIAL for monitoring but also ESSENTIAL for the RA PRIOR to releases, as explained above.

p.49 Risk management 2nd para. Why are the CBD (draft) requirements not mentioned until now? They are not merely MONITORING requirements, but requirements for the RA. Why are they not cited in full? Why are effects on non-target organisms and human immunity not included (see also the draft EFSA guidance)? Again it is beyond belief that these requirements are apparently not deemed relevant until phase 4.

p.49 last para. Monitoring must include other vector species. Post-implementation is REQUIRED (it is a legal requirement in the EU). Health monitoring is REQUIRED to monitor for potential adverse

effects on human health (this is likely to be required by biosafety laws and needed to meet ethical requirements).

p.50 1st para. Again, why is this phase4??? E.g. the draft CBD requirements state that factors that must be considered in the RA (i.e. PRIOR to open releases) include: "Whether the release of an LM mosquito would affect pest control activities, such as the use of personal protection and insecticides that control other vectors." As noted above, GMM releases may conflict with some other control measures.

p.50 3rd para. Again, why is disease surveillance delayed to phase 4? It is an essential ethical and biosafety requirement for any open releases in populated areas.

p.50 4th para and final para. Dispersal must include human dispersal, as noted above. Again, this is not just a monitoring/risk management issue to be left to phase 4! Ditto, cross-border movements. Access to environmental information requirements should also apply to neighbouring states i.e. they should be consulted on risk assessments etc.

p.51 Some lessons should be learned from Oxitec's failure to comply with transboundary notification requirements to date. See: Oxitec's Genetically Modified Mosquitoes: Ongoing Concerns. GeneWatch UK. August 2012. http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf Also, Brazil has still not supplied any information to the Biosafety Clearing House about open releases of Oxitec's GM mosquitoes there, which began back in February 2011 (the entire risk assessment was withheld as commercially confidential in Brazil) i.e. the requirements are in practice a joke.

p. 51 Heading "Consider the need for independent safety review": delete the first four words!

p.51 Biosafety Capacity. The word "transparent" is a joke in relation to all Oxitec's open releases of GMM to date. More needs to be said about transparency requirements and best practice (e.g. Aarhus Convention). Input from stakeholder groups and communities also requires time, resources and capacity.

p.51 Does "independent international expertise" mean Oxitec will review its own risk assessments as well as trying to write its own guidance? Rules on conflicts-of-interest need to be adopted and followed.

p.52 The endpoint "causes more harm" than current practice is incorrect: this is not the purpose of a risk assessment. This idea contradicts other parts of this document which accepts that the decision making process will include consideration of efficacy, cost-effectiveness, alternatives etc. Further, it misinterprets what a risk assessment is. The document would benefit from a separate section about how the various assessment aspects and consideration of alternatives will inform the final decision on implementation.

p.53. Missing issues from Table 3.1 include tests of conditionality, stability, resistance mechanisms, disease transmission properties, marker reliability. Tests under different environmental conditions are required, e.g. different temperatures, feeding conditions (see e.g. Marelli et al., 2007). A table on example studies for CAGED trials is entirely missing and should also include e.g. studies on larval competition and density dependence in the relevant receiving environment(s) and effects on non-target organisms. Details on the required baseline studies of ecology, entomology and disease transmission (which are needed prior to open releases) are also missing. Table 3.2 repeatedly refers

to modelling but does not appear to require that any of these models are validated (!). Validation of models of baseline population dynamics and disease transmission will be needed PRIOR to any open releases if the scientific programme is to have any credibility. Missing issues in the Table 3.2 include studies of non-target organisms, including non-target vectors, and any studies of the human population and impacts on transmission of disease (!). Release ratios must also be reported. The authors are recommended to study responses to the consultation on the draft EFSA guidance in the EU, as well as the draft CBD guidance, to ensure that all the relevant issues are included.

12) Do you have any specific questions on ethics and engagement?

The standard of this chapter is inadequate and it needs a complete rewrite. Its main purpose seems to be to undermine any mechanism in which local people are actually given any rights to comment or influence decision-making on the ground. The proposed so-called "engagement" exercises amount to a PR exercise of the kind Oxitec conducted in Brazil, which is the opposite of informed consent and undermines the ethical principles established in the Helsinki Declaration and elsewhere. Further, fully informed consent cannot be given if nobody is informed: failure to publish or consult on risk assessments and failure to publish research protocols is therefore unethical (this has been a systemic problem with Oxitec's releases to date, where even the legislative requirements to copy risk assessments to the UK and EU authorities were not complied with). Environmental justice is mentioned once (page 69) but the Aarhus Convention which establishes international standards in this area: including access to environmental information and access to justice is not even mentioned. The requirement for ethical oversight is here replaced by drivel about ethical reflection, which apparently means that the commercial company and researchers agree their own ethical standards, a practice universally regarded as poor and unacceptable. The discussion of "standard of care" then assumes that research ethics committees will impose standards (which indeed, they will have to, because Oxitec has not).

Fully informed consent and ethical oversight is required for all open release trials of GMM and the argument that it was not needed for Oxitec's trials to date is a weakly argued post-hoc justification for an unacceptable situation. The purpose of the trials is to affect disease transmission and incidence and therefore this is medical research and the people in the release area need to be fully informed as required by Article of the Helsinki Declaration: "*In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed*". Further, the design and performance of each research study involving human subjects must be clearly described in a research protocol (Article 13) and the research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins (Article 15). See also: Macer D., 2005. Ethical, legal and social issues of genetically modifying insect vectors for public health. Insect Biochemistry and Molecular Biology 35, 649-660; Macer D (2003) Ethical, legal and social issues of genetically modified disease vectors in public health. WHO reference number: TDR/STR/SEB/ST/03.1. WHO reference number: TDR/STR/SEB/ST/03.1. Further, practical difficulties are likely to arise in Brazil if health data is collected in future trials (where the

authors seem to accept ethical requirements will then kick in!) due to the fact that people were misled into believing that GMM were a "solution" rather than an experiment and not fully informed before the first open releases took place.

If public and private investors have already made a prior decision to invest in commercialising a particular technology, public engagement exercises risk becoming simply PR exercises which fail to take concerns into account. See e.g. Participatory Science and Scientific Participation: The role of Civil Society Organisations in decision-making about novel developments in biotechnologies. Final Report. October 2008. PSx2 Project. EC 6th Framework Programme. Consiglio dei Diritti Genetici, Universität Bremen, GENET, GeneWatch UK, CRIIGEN, Eestimaa Looduse Fond, Université de Caen, Università di Perugia, Consejo Superior de Investigaciones Cientificas.
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/PSX2_final_20report.pdf
Where a discussion of engagement might also have been helpful is in discussing public involvement in research trajectories and priorities for funding, implementation and R&D. The recent Nuffield Council on Bioethics report on novel biotechnologies may have been useful in this regard: http://www.nuffieldbioethics.org/emerging-biotechnologies .

13) Do you have any specific questions on regulatory frameworks?

p.85. Summary. It is frankly not a good start to begin with a summary which opposes the use of a precautionary approach, which is a requirement of the CPB and a legal requirement in many countries (including in EU legislation for the deliberate open release of GMOs). Risk assessments are therefore likely to be legally required to follow the precautionary principle in most countries: what kind of "guidance" seeks to rewrite existing Conventions and legislative requirements? Ramblings about "public health uses" as if they are not-for-profit is hardly relevant when all open releases to date (and many planned releases) are by the for-profit company Oxitec. Regulatory agencies currently only exist for risk assessment for open releases of GMOs, NOT for efficacy assessment. This is because assessment of potential benefits and decisions whether to plant GM crops or not have been left to individual farmers acting as customers for GM crops. The idea that potential health benefits must be somehow taken into account WITHIN the risk assessment process is a bizarre one and conflicts with existing regulatory requirements (as explained above). Of course the customer (often a developing country government in the case of public health applications) must consider potential benefits (or lack of them) and alternatives prior to making a decision on whether or not to implement a programme of GMM releases. However this requires consideration of EFFICACY, which is not currently part of the regulatory assessment process for GMOs.

p.85 penultimate para. "Without conflict of interest" is important: but a process is needed to ensure this and WHO/FNIH should ensure this for the Guidance too!

p.85 last para. Again, benefits appear to be being assumed here, without any consideration of efficacy.

p.86 2nd para. This is completely wrong: benefit assessments are NOT part of the regulatory risk assessment process. Transparency is not discussed elsewhere in the Guidance.

p.87 As noted above human subjects are exposed during open releases of GMMs to processes which are expected to benefit their health but which might also be harmful to their health. Therefore an ethics committee and fully informed consent is required. This is NOT dependent on whether or not blood samples or other health monitoring is undertaken since the hazards due to the GMM releases are the same whether or not samples are taken. Experimental releases of GMM should in any case

require health monitoring as part of the monitoring plan, otherwise unexpected adverse impacts on human health will not be identified.

p.88 First para. The idea that GM animals can be regulated under the definition of a biopesticide is unique to the US. There have already been problems stretching this definition to GM salmon engineered to produce growth hormone, but for GMM the concept is even less relevant since the mechanisms of action (both potential benefits and harms) occur largely indirectly via environmental interactions, not through the direct action of the expressed protein on the target disease.

p.88 The lead author of this chapter Robert Rose was closely involved in USDA APHIS' attempts to regulate Oxitec's GM bollworms, and in the drafting of the 2009 EIS referred to on page 92. This EIS has been strongly criticised in the scientific literature (Reeves et al., 2012) and USDA APHIS has been required to entirely rewrite its approach to regulating GM insects as a result of a USDA Office of Inspector General report in 2011, which argued that USDA APHIS' controls over GM insect research were inadequate and that regulations needed to be strengthened. The report also criticised APHIS' Center for Plant Health Science Technology (CPHST) for lack of formal control over grant decsiions during the period it was funding Oxitec. The report's recommendations were accepted by APHIS, requiring it to clarify its role, draft specific GM insect regulations, and make more transparent research funding decisions. See: USDA (2011) Controls over Genetically Engineered Animal and Insect Research. United States Department of Agriculture Office of Inspector General. 31st May 2011. http://www.usda.gov/oig/webdocs/50601-16-TE.pdf . Given the lead author on this section of the WHO/FNIH draft Guidance Framework, it is perhaps not surprising that all this rather important information has been omitted from the discussion! Regulation of Oxitec's proposed GMM trials in Florida have now passed to the FDA but the existing regulation is clearly inadequate (see above). A more credible author for this chapter might have been expected to cite the critique of the US regulatory system published by Pew in 2004. Pew Initiative on Food and Biotechnology (2004). Bugs in the System? Issues in the science and regulation of genetically modified insects (Washington, DC, Pew Initiative on Food and Biotechnology). http://www.pewtrusts.org/our_work_report_detail.aspx?id=17984 and the associated conference proceedings: Biotech Bugs. Proceedings from a conference sponsored by the Pew Initiative on Food and Biotechnology, September 20—21, 2004, Washington D.C. http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Summaries_-_reports_and_pubs/Bugs-English-Final.pdf . The authors should also note that the US is not a Party to the Cartegena Protocol on Biosafety and is therefore not a good model for other countries.

p.88 last para, should note there is no specific legislation (or final guidance for risk assessment) for GMMs.

p.89 First para. As noted, this approach to GM animals is limited to the US and has serious limitations, which are exacerbated in the case of GMMs.

p.89 2nd para. Wording of Cartagena Protocol includes "taking into account human health" and this should be mentioned.

p.89 3rd para. Conflicts of interest are not only a problem in developing countries!!!

p.89 ALL GMM applications raise cross-border issues because self-limiting GMM may still survive and be transported across borders (e.g. through human movements).

p. 92. The section on the 2009 USDA Environmental Impact Statement (EIS) should note that open release experiments using GM fluorescent bollworms were terminated and Oxitec's RIDL bollworms

were never released or integrated into the pest control program, which continues to be successful using traditional irradiated SIT. The 2011 USDA Office of Inspector General report cited above (unaccountably forgotten by the author who wrote the EIS!) supersedes the EIS and requires the whole system of regulation to be re-written. The critique of the EIS in Reeves et al. (2012), which describes it as "scientifically deficient" should also be mentioned!

p.93 2nd para. It would be nice if risk assessments were not only written but also published and consulted on! The provisions of the Aarhus Convention require that parties do this.

p.93 Self-limiting does not mean no risk. Why not cite some actual regulatory requirements (e.g. Directive 2001/18/EC) instead of making them up? When transboundary movement is POSSIBLE information and consultation requirements are needed for adjacent states.

p.94 1st para. Phase 2 and/or 3 WILL require assessment of impact on nontarget species. Post-market monitoring will be a regulatory requirement in many jurisdictions (it is in the EU).

p.94 2nd para, last sentence. The phrase "with genetic constructs capable of spreading within a vector population" should be deleted as hazards may also be posed through other mechanisms.

p.94 3rd para. The precautionary principle is a legal requirement in many countries and GMM are a novel technology which may give rise to unexpected or unknown risks. GMM are not "most often" developed by non-profit organisations: the only ones that have been released and are currently proposed for further release are produced by the FOR-PROFIT company Oxitec. Potential benefits should NOT be part of risk assessment, which has a clearly defined regulatory purpose. But an efficacy assessment is an important element of the decision-making process.

p.94. last para (and first para p.95). Conflicts-of-interest should have been declared by those involved in drafting this guidanceand WHO-TDR/FNIH should have a procedure in place to eliminate conflicts-of-interest from biasing guidance or other important documents. Perhaps consultant Robert Rose would like to make a start by declaring his own interests? For more on conflicts-of-interest, see: Genetically-modified insects: under whose control? GeneWatch UK, Testbiotech, Berne Declaration, SwissAid, Corporate Europe Observatory. November 2012. http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Regnbrief_fin2.pdf

p.95 2nd para. Litigation. Why nothing on liability?

p.95 3rd para. Conflicts-of-interest in capacity building might merit some discussion given the role of Oxitec in the WHO-TDR funded Mosqguide project. Why did this project persuade CTNBio to stop drafting GM insect guidance in Brazil and press ahead with trials WITHOUT building capacity? Why is Oxitec doing all the so-called "capacity building" when it appears to be incapable of following legal or ethical requirements? Who will regulate efficacy?

p.95 4th para. Use of "not for profit" again. TOTALLY UNTRUE!

p.96 2nd para. Most transboundary movements may not be "autonomous" but facilitated by human movement. These need to be considered as this is how existing mosquito species have spread and become established around the world.

p.97 Density dependence and other factors tend to make control of mosquitoes much more complicated.

p.98 Mosqguide persuaded Brazil to stop developing the GM insect regulation and release Oxitec's GMM without any specific regulation! Why? Also the risk assessment wasn't published and it wasn't sent to the UK and EU authorities when required under EU law. Nothing was sent to the Biosafety Clearing House. Informed consent was not sought and can't exist if there is no information!

p.100 USA. Penultimate para. NO: the APHIS Guidance has been criticised by the 2011 USDA Office of Inspector General report cited above and will be re-written. Oxitec's GMM application for Florida is now with the FDA.

p.101 First para includes lots of rubbish about the USDA APHIS EIS which is "scientifically deficient" and no longer the basis for assessment of any GM insect or GMM in the United States as explained above (but was written by Robert Rose!).

p.101 It would be useful to mention EU transboundary notification requirements, which require a risk assessment that meets EU standards. These (and Oxitec's failure to meet them) are discussed in more detail in: Oxitec's Genetically Modified Mosquitoes: Ongoing Concerns. GeneWatch UK. August 2012.
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf .

p.103. Should mention that the US is not a party to the Cartegena Protocol (and nor is the Cayman Islands, where the first GMM were released).

p.104 last para. Only Malaysia submitted information to the Biosafety Clearing House in relation to GMM releases to date. The Cayman Islands is not a Party and Brazil has simply ignored the requirements and not submitted anything. GeneWatch UK and some UK parliamentarians eventually obtained the risk assessments for Brazil (redacted) and the Cayman Islands via the UK and EU authorities: they are of poor quality and do not meet the required EU standards. There was no consultation on the risk assessments.

p.105 Why is Article 20 (Information Sharing) omitted? Why are several aspects highlighted by the Ad Hoc group omitted from the biosafety chapter in this document? E.g. "new or more vigorous pests" and "evolutionary responses"?

p.109 Is this document trying to claim that Mosqguide really developed "best practice"???! This is a joke. The use of the word "transparency" is also a joke: how is not publishing risk assessments "transparent"???. It might be helpful in general to highlight to the reader how many of these so-called guidelines were actually written by Oxitec: see: Genetically-modified insects: under whose control? GeneWatch UK, Testbiotech, Berne Declaration, SwissAid, Corporate Europe Observatory. November 2012.
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Regnbrief_fin2.pdf

p.110 The reference to the EIS again omits to mention that this has been binned and superseded by: USDA (2011) Controls over Genetically Engineered Animal and Insect Research. United States Department of Agriculture Office of Inspector General. 31st May 2011.
http://www.usda.gov/oig/webdocs/50601-16-TE.pdf . And that it is scientifically deficient. See: Reeves, R.G. et al., 2012. Scientific Standards and the Regulation of Genetically Modified Insects M. J. Lehane, ed. PLoS Neglected Tropical Diseases, 6(1), p.e1502.
http://www.ploscollections.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0001502;jsessionid=C3DC4FD0650E395B0FD63D275A9703B5#pntd-0001502-g001

p.110 The document should say explicitly that Macer's view is that INFORMED CONSENT IS REQUIRED before GMM trials and this was until recently the WHO's position. This document does a U-turn on this for no valid reason other than the fact that Oxitec didn't seek informed consent for its own trials and the WHO is implicated in this unethical decision via the Mosqguide project. Is this ethical? NO.

p.111 3rd para. Caged trials should be REQUIRED prior to open releases. This will be a legal requirement in the EU and probably elsewhere.

p.11 This paragraph is so biased and selective! If GMM have poor efficacy they won't avoid impacts of other control measures will they? There is nothing in this document about the need to restrict GMM to authorised receiving environments at all (whether this is other states or simply regions with inappropriate ecological, entomological or human/disease characteristics). This is a major omission.

General comments
14) Do you have any other comments?

Yes. GeneWatch UK is extremely concerned that no Declarations of Interest have been published by members of the team developing the guidance framework, nor has any action been taken by WHO-TDR to ensure that the process of developing the Framework is not biased by conflicts-of-interest. For example, Dr Michael Bonsall has been funded by the UK Biotechnology and Biosciences Research Council (BBRSC) to work with Oxitec to develop regulations which allow its products to be commercialised. See: Grant No. BB/H01814X/1 Integrating ecology and genetics for insect pest control. Dr Michael Bonsall University of Oxford £322,120. http://www.bbsrc.ac.uk/PA/grants/AwardDetails.aspx?FundingReference=BB%2fH01814X%2f1 . Dr Bonsall works for Oxford University which is an investor in Oxitec, via Oxford Spin-Out Equity Management (http://www.osem.ox.ac.uk/), and which therefore has a commercial interest in favourable regulation. Dr Bonsall was required to leave the room when a proposal to release GM diamond back moths produced by Oxitec was discussed by the UK Advisory Committee on Releases to the Environment (ACRE). See: ACRE (2011) Advisory Committee on Releases to the Environment: Minutes of the 134th Meeting of ACRE at Nobel House, London, Thursday, 1st December 2011. http://www.defra.gov.uk/acre/files/ACREMINUTES20111201.pdf . Yet Dr Bonsall has chaired the WHO-TDR/FNIH Biosafety Working Group.

Preparation of the regulatory section of the draft guidance was led by the consultant Robert Rose, who also assisted in the preparation of the 2008 USDA APHIS Environmental Impact Statement (EIS) on the use of GM insects in plant pest programs. This EIS has been strongly criticised by independent scientists and, in 2011, the USDA Office of Inspector General issued a report arguing that USDA APHIS' controls over GM insect research were inadequate and that regulations needed to be strengthened. There are no declarations-of-interest published to accompany this draft Guidance Framework and WHO-TDR/FNIH do not appear to have adopted any procedure to deal with conflicts-of-interest, therefore it is impossible to know whether Rose has other clients who might have a vested interest in the adoption of guidance which seeks to undermine the precautionary principle and existing risk assessment processes.

John Mumford of Imperial College, a member of the core working group, worked directly with Oxitec as part of the Mosqguide project on releases of GMM in Brazil, where the risk assessment was withheld as commercially confidential, regulators were persuaded to press ahead with trials before guidance on GM insects was adopted and without prior caged trials in relevant environments, the process of seeking informed consent was replaced by a PR exercise involving a jingle claiming Oxitec's GM mosquitoes are "the solution" to dengue, and no information was submitted to the

Biosafety Clearing House, in contravention of the Cartegena Protocol. For a project that was supposed to be developing “best practice” this is pretty bad. For more details see: Oxitec’s Genetically Modified Mosquitoes: Ongoing Concerns. GeneWatch UK. August 2012. http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_unansweredQs_fin.pdf . No “lessons learned” from allowing Oxitec free hand to effectively run the Mosqguide project using WHO-TDR funds appear to have been published or taken into account in the development of this document.

For more details on conflicts-of-interest, see: Genetically-modified insects: under whose control? GeneWatch UK, Testbiotech, Berne Declaration, SwissAid, Corporate Europe Observatory. November 2012.
http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Regnbrief_fin2.pdf

Removal of conflicts of interest is essential prior to a complete rewriting of the document to provide Guidance on legal and ethical requirements, rather than seek to undermine them. Further consultation will then be necessary if the document is to have any credibility.

It has been difficult to comment on the document in a comprehensive way in the time available, due to the large numbers of errors and omissions. Further consultation will be essential if the final document is to have any credibility.

15) Thank you for your time!