AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

Guidelines for Compliance Monitoring and Inspection of Activities involving Genetically Modified Mosquitoes

West Africa Integrated Vector Management Programme

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About The AU, AUDA-NEPAD and WAHO

The African Union (AU)

The African Union (AU) is a body of 55 member states that make up the countries of the African Continent. It was officially launched in 2002 as a successor to the Organization of African Unity (OAU), which ran from 1963 to1999. The decision to re-launch Africa's pan-African organisation was the outcome of a consensus by African leaders that in order to realise Africa's potential, there was a need to re-focus attention from the fight for decolonisation and ridding the continent of apartheid hitherto pursued under the OAU, towards increased cooperation and integration of African states to drive Africa's growth and economic development. The AU is guided by its vision of *An integrated, prosperous and peaceful Africa, driven by its own citizens and representing a dynamic force in the global arena [1].*

To realise this vision, the Africa Union developed and adopted a 50-year strategic plan called Agenda 2063 [2]. Agenda 2063 is the continent's strategic framework that aims to deliver on its goal for inclusive and sustainable development and is a concrete manifestation of the pan-African drive for unity, self-determination, freedom, progress and collective prosperity pursued under Pan-Africanism and African Renaissance.

The AU has been steadfast in proposing more enabling and science-based approaches to the challenges of the continent. Its report on gene drives clearly embraces the technology as a realistic option for effective disease control. A constructive development along this path was witnessed at the 29th Ordinary Session of Heads of State and Government of the African Union in Addis Ababa, where pursuant to Decision *Assembly/AU/Dec.649 (XXIX),* the session embraced the gene drive technology as a realistic option for malaria control. The session, in its decision, requested the African Union Commission (AUC), West African Health Organization (WAHO) and African Union Development Agency-New Partnership for Africa's Development (AUDA-NEPAD) to collectively support the initiative [3].

In 2018, through recommendations of the African ministers responsible for science and technology *EX.CL/Dec. 987(XXXII),* the Executive Council of the African Union encouraged member states to harness emerging technologies, including gene drive, in their development initiatives [4].

The decisions above have offered solid policy statements for the continent regarding gene drives for human health purposes, which have impacted discussions in AU member states. It is a basis for a harmonised approach for Africa in the development of policy regulations and guidelines such as this to facilitate the responsible and safe application of the technologies for research and subsequent deployment.

The African Union Development Agency - NEPAD (AUDA-NEPAD)

At the 31st Ordinary Session of the Assembly of African Union Heads of State and Government held in Nouakchott, Mauritania from 25th June to 2nd July 2018, the Heads of State and Government approved the transformation of the New Partnership for Africa's Development (NEPAD) Planning and Coordinating Agency into the African Union Development Agency (AUDA) as the technical body of the African Union with its own legal identity, defined by its own statute [6]. The objectives of AUDA-NEPAD are to: a) coordinate and execute priority regional and continental projects to promote regional integration towards the accelerated realisation of Agenda 2063; b) strengthen capacity of African Union Member States and regional bodies; c) advance knowledge-based advisory support; d) undertake the full range of resource mobilisation; and e) serve as the continent's technical interface with all Africa's development stakeholders and development partners.

The West African Health Organization (WAHO)

The West African Health Organization (WAHO) was established in 1987 when the Heads of State and Government from all fifteen countries in the Economic Community of West African States (ECOWAS) adopted and thereafter ratified the protocol for its creation. WAHO has transcended linguistic borders and hurdles in the sub-region to serve all fifteen ECOWAS Member States. The protocol grants WAHO the status of a specialised agency of ECOWAS and, as guided by its mission statement, 'the attainment of the highest possible standard and protection."

The regional agency is charged with the responsibility of safeguarding the health of the peoples in the sub-region through initiation and harmonisation of relevant policies of Member States, pooling of resources, and in cooperation with one another, maintaining a collective and strategic focus on important health problems of the sub-region.

WAHO has, through its strategic programmes, undertaken measures to combat malaria, malnutrition, HIV/AIDS as well as maternal and infant mortality. It has also spearheaded the prevention of blindness, increased access to medicines and vaccines, epidemiological surveillance as well as training and health information management in the sub-region.

Through its second strategic plan, WAHO is currently implementing various cutting-edge programmes in the sub-region to improve the overall health systems, ensure high-quality health services, develop sustainable financing of health and support institutional development within WAHO itself.

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Acronyms

AU	African Union
AUC	African Union Commission
AUDA-NEPAD	African Union Development Agency-New Partnership for Africa's Development
BO	Biosafety Officer
CFTs	Confined Field Trials
CMI	Compliance Monitoring and Inspection
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats- CRISPR-associated protein 9
ECOWAS	Economic Community of West African States
GMM	Genetically Modified Mosquitoes
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
IBC	Institutional Biosafety Committee
NBA	National Biosafety Agency
NBC	National Biosafety Committee
NCA	National Competent Authority
PI	Principal Investigator
SOPs	Standard Operating Procedures
T&Cs	Terms and Conditions
TM	Trial Manager
WAHO	West African Health Organization
WA-IVM	West Africa Integrated Vector Management

Glossary

Activity: refers to conducting, making, studying, testing or use of any type of GMM in the laboratory, population cage, confined field trials or deployment in limited or large scales.

Arthropod: an invertebrate animal of the large phylum Arthropoda, such as an insect, spider, or crustacean, that are of relevance in health.

Biosafety Officer: in the operation of this guideline, a Biosafety officer develops and participates in programs to promote safe practices in a GMM activity, procedures, and proper use of containment equipment and facilities. He/she stimulates responsible activities among workers and provides advice on laboratory design and research safety procedures.

Compliance: the act of maintaining standards specified in applicable statutory provisions, Standard Operating Procedures (SOPs), and Terms and Conditions (T&Cs) of approval for the purpose of minimising potential adverse effects arising from a GMM activity.

Compliance monitoring: the act of carrying out surveillance on and/or recording of anomalies from those permitted in a GMM activity for the purpose of assessing compliance with defined standards or conditions established in relevant regulatory instruments.

Gene Drive (three dimensions in its definition): - a process that promotes or favours the biased inheritance of certain genes from generation to generation - any genetic element able to bias its inheritance within a population. - a tool to effect certain changes in a population Phenomenon or Process: A gene drive is a phenomenon of biased inheritance in which the prevalence of a genetic element (natural or synthetic) or specific alternate form of a gene (allele) is increased, even in the presence of some fitness cost. This leads to the preferential increase of a specific genotype that may determine a specific phenotype from one generation to the next and potentially spread throughout a population. In other words, a gene drive is a process that promotes or favours the biased inheritance of certain genes from generation to generation. Material Object: A gene drive is composed of one or more genetic elements that can cause the process of biased inheritance in its favour. A gene drive is any genetic element able to bias its inheritance within a population.

Intention: A gene drive may be intended as a management tool to effect certain changes in a population. A gene drive may include additional "cargo" elements, in addition to the drive components, that are intended to introduce new trait(s) into an interbreeding population so as to effect a change in the characteristics of the population. A gene drive also may cause effects directly, for example, by inserting into and disrupting a target gene. www.pnas.org/cgi/doi/10.1073/pnas.2020417117

Genetically Modified Mosquitoes: Mosquitoes genetically modified to rapidly spread a desired trait into related species to attain a specific goal such as malaria control.

Inspection: an act by the National Competent Authority (NCA) of conducting an official review of documents, facilities, records, and any other information resources that are deemed by the NCA to be related to the GMM activity, and to determine whether the PI is following SOPs, Terms and Conditions of approval and other applicable statutory provisions.

Inspector: a person or an entity tasked with the duty of closely examining a GMM activity for the purpose of ensuring compliance as per the statutory provisions of a given country

Standard Operating Procedure: the established or prescribed methods to be followed routinely for the performance of designated operations or in designated situations

Terms and Conditions: legally binding requirements specified by a regulatory in a GMM activity permits that need to be observed by an operator of a GMM activity

Scope

This document is meant to serve as a guideline on Compliance Monitoring and Inspection (CMI) for biosafety regulators at institutional and national levels, as well as any personnel involved in managing and implementing the use of Genetically Modified Mosquitoes (GMM) in health. The guidance does not cover other GMMs in use outside the health sector, which are meant to ensure safety as per the applicable statutory provisions of a given country.

The guideline applies to CMI duties of GMM activities under different phases of development, ranging from laboratory to cage population, as well as confined field trials and field-scale deployment. It aims to provide a regional framework to standardise and implement CMI of a GMM activity in Africa to ensure safety.

Introduction

Gene drive is a system of biased inheritance in sexually reproducing organisms that enable the rapid and extensive spread of gene drive bearing traits in the population of the organisms in question [7]. Gene drive systems have been known for decades, but recent advancements of Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR-Cas9) genome editing techniques have accelerated its applications in health, agriculture and conservation. These systems offer unprecedented capabilities for modifying or suppressing populations of insects such as disease-transmitting mosquitoes [5,6]. Both of these features have been demonstrated in multiple studies in the laboratory. In addition, mathematical models also show that considerable suppression of vector populations can be achieved within a few years of using a female sterility gene drive, though the impact is likely to vary from one place to the other. [8, 9].

However, the potential risks associated with this technology have not been fully understood. It has therefore been strongly suggested that the development and deployment of Genetically Modified Mosquitoes should follow a precautionary approach, with stepwise testing under strict regulatory oversight to minimise or avoid potentially harmful effects to human, animal or environmental health [6,12]. Since the experience with regulatory oversight of gene drives is still in its infancy, AUDA-NEPAD and ECOWAS, through the West Africa Integrated Vector Management (WA-IVM) Programme, are developing guidelines to support responsible conduct of activities involving the technology. The guidelines will ensure the safety of the technology and help in building public confidence in the adequacy of the required oversight.

This specific document presents the guidelines necessary to ensure compliance monitoring and inspection of activities involving the use of Genetically Modified Mosquitoes in health and the environment.

Responsibilities

There should be accredited institutions in existence with a duly accredited Institutional Biosafety Committee (IBC) to spearhead any activity involving GMMs since a complete application and maintenance of an active protocol requires a laboratory facility safety review for a designated research area at an institutional level. An IBC has an important role in ensuring that such research facilities meet the required standards for biosafety.

The IBC of the institution conducting a GMM activity takes the primary responsibility at the institutional level for monitoring the compliance with statutory provisions, T&Cs and SOPs.

Inspection should be done either routinely or unannounced to make sure that statutory provisions are observed and the safety of the environment and the public are ensured. As per this guideline, the national duty of inspection falls under the purview of the National Biosafety Regulator. Inspectors will make planned periodic or impromptu inspections of a GMM activity to attest compliance and also audit the procedures laid down by the IBC.

Purpose of Compliance Monitoring and Inspection

Compliance monitoring and duties of the IBC

Compliance monitoring is one of the key duties of the IBC with the aim of ensuring that GMM activities are carried out in line with the biosafety laws and regulations of a particular country. It encompasses all routine regulatory oversight activities performed to determine whether GMM activities in the laboratory, population cages, confined field trials or limited or large-scale environmental releases follow applicable law(s) and regulation(s) of a particular jurisdiction.

IBC duties in monitoring compliance include

- Formulating and implementing strategies for compliance monitoring
- Monitoring off-site compliance, including data collection, review, reporting, program coordination, oversight and provision of support
- Monitoring on-site compliance at facilities such as the laboratory, population cages and confined field trials
- Interacting with and providing feedback to the Principal Investigator (PI) and Trial Manager (TM) indicating the identified adequacy or shortfalls in procedures, facilities or follow-ups to make sure that proper safeguards are in place and corrective measures are taken when necessary.
- Ascertaining that the phased activity (e.g., laboratory study, population cage study or confined field trial) of the GMM is being conducted in line with the relevant guidelines and legislation.
- Determining that the said activity follows the terms and conditions of the approved protocol, applicable SOPs, and regulatory requirements usually stated as permit conditions
- Periodically updating in writing, the NCA on the regulatory status of an approved GMM activity as required by the NCA

Inspection and duties of inspectors

Inspection of GMM facilities, trials and other activities is an integral part of periodic oversight of safety compliance programs for activities involving GMM. It is an important tool for officially assessing compliance with legal and regulatory requirements of a specific jurisdiction under which the GMM activities are being conducted.

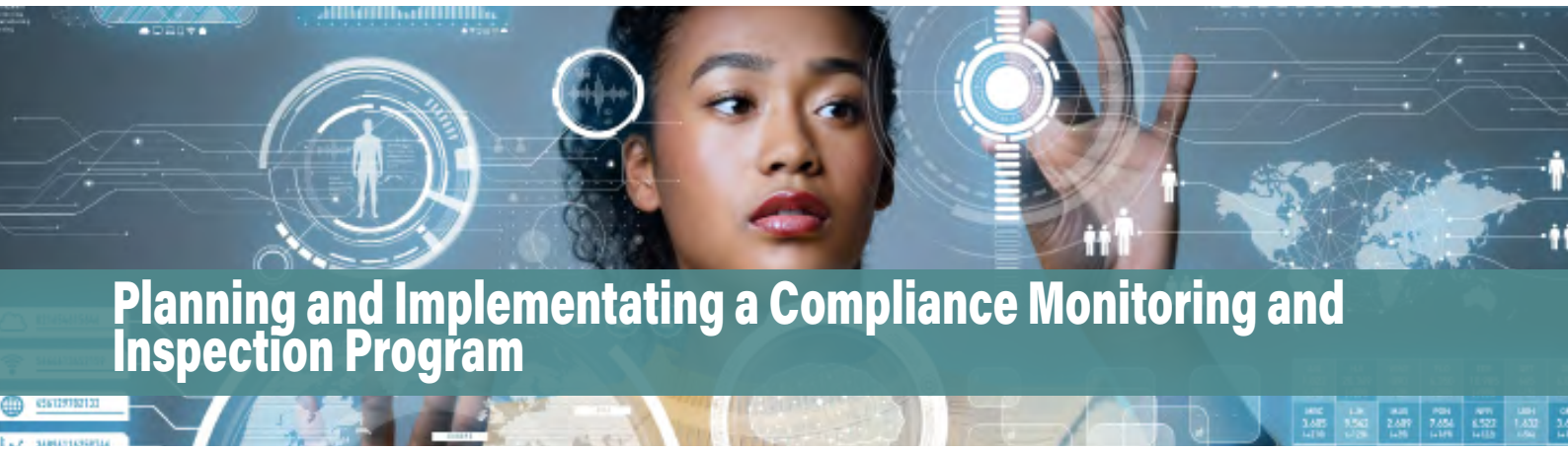
Inspections are visits to a facility or site of a GMM activity, maintenance or storage for the purpose of gathering information to determine whether it is in compliance with applicable statutory provisions, SOPs, and T&Cs of approval. The inspections, therefore, also contribute towards minimising potential adverse effects arising from the activity of GMM. The intensity and scope of an inspection can range from a brief walk-through and review of records to the inspection of containment facilities or even an inspection with extensive physical sample collection in case of later phases of GMM operations such as field releases.

The inspectors should have the skills and professional composition necessary for undertaking their inspection duties matching the needs of each phase of activity. For instance, the professional profile, skills and experiences required for inspection of laboratory experiments with GMM can vary substantially from those required for inspecting activities in confined trials or deployment in limited or broader field scales. Whereas oversight of GMM activities in the laboratories may require skills in molecular biology, activities such as confined field trials (CFTs) and beyond may require an in-depth analysis and understanding of the potential dynamics and impacts at an ecosystem level.

The duties of inspectors shall be:

- Performing periodic closer evaluation of a GMM activity to ascertain whether statutory provisions are being observed, including review of permits (giving due attention to T&Cs), data, and other documentation
- Receiving and providing appropriate training and support
- Carrying out pre-inspection activities such as obtaining general site information before entering the facility or site
- Interviewing representatives of facilities or sites

- Reviewing records, SOPs, permits and reports
- Observing facility or site operations
- Providing feedback to IBCs and Biosafety Officer (BO) to encourage compliance or fixing minor issues identified.
- Providing warning or recommending to the National Biosafety Agency (NBA) to order discontinuation in a GMM activity in case of major or critical lack of adherence to statutory provisions, relevant guidelines, SOPs and other important GMM regulatory instruments has occurred.



Planning and Implementating a Compliance Monitoring and Inspection Program

Planning and Implementation of Compliance Monitoring

The PI shall be responsible for producing a written compliance monitoring plan with the support of the IBC quarterly. The IBC or an individual tasked with compliance monitoring duties such as a Biosafety Officer should regularly monitor a GMM activity in an institution conducting such activity. The IBC should regularly give a written report regarding the regulatory status of the GMM activity to the management of the institution in which it is conducted. Such updates should include the adequacy or shortfall of the system and the support required to maintain or improve the inadequacy of the risk management system for a GMM activity. In addition, the IBC should regularly report to the NBA or other equivalent bodies as required by the NBA.

However, in case of serious anomaly, the institutional Biosafety Officer shall be required to report immediately to the NBA within the timeframe specified in the Regulations for appropriate safety remedial measures to be taken.

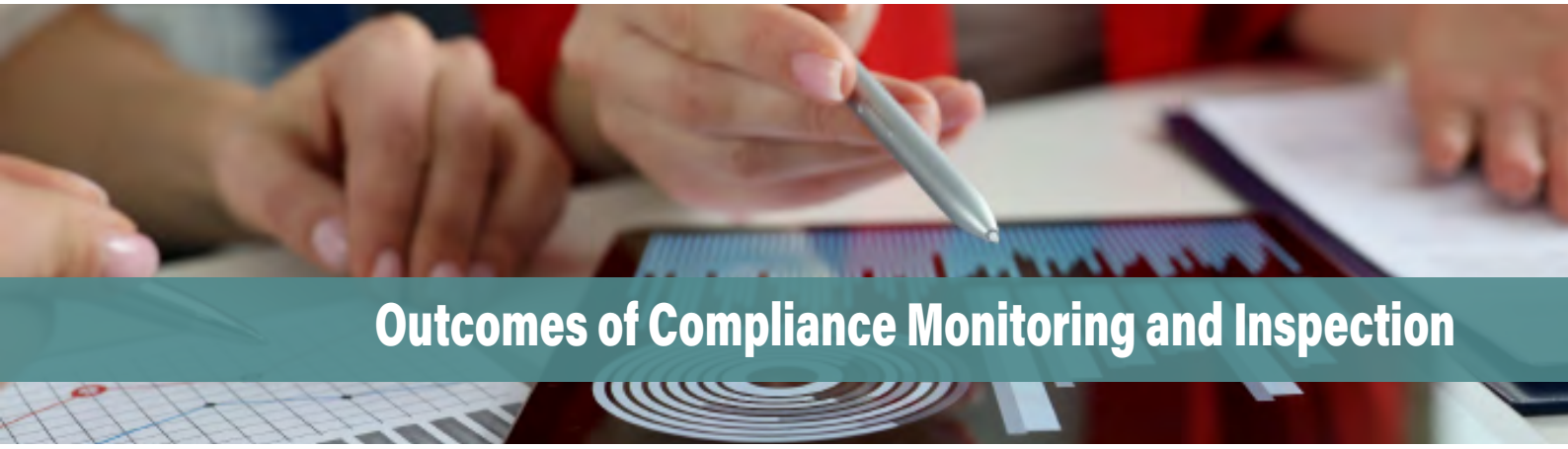
Planning and Implementation of compliance Inspection

A compliance inspection is a systematic process used to determine if the conditions or requirements of a licence, approval or legislative instrument are being met. A proactive compliance inspection program assists personnel involved at all levels of GMM activity to meet their statutory requirements, respond to common complaints and maintain a positive monitoring presence with GMM operations that may pose potential concerns to human, animal or environmental health if not carried out as required in the permit.

In effecting its statutory duties, the NCA should perform, observe or enforce the following to discharge its regulatory duty with respect to inspection of a GMM activity:

- Develop a strategy and plan for inspection of all the activities pertaining to GMM in order to ascertain that the activity is being carried out as per the terms of approval. Checklists and SOPs are particularly useful in this regard.
- Inspectors should have a well-defined plan, data points, information needs and measurable outcomes in order to help ascertain that GMM inspection objectives are met.
- Ensure that the frequency and depth of the inspections are adequate to meet the objective of making sure that the GMM activity is being conducted in line with the Terms and Conditions granted to carry out the said GMM activity.

- Undertake regular inspection to ensure that the GMM activity is being conducted in a manner that ensures safety to the environment, human and animal health but should not unnecessarily be overbearing to constrain the normal conduct of the said GMM activity. The inspectors should ensure that their duties and privileges of access to premises, facilities, trial objects, data and information are meant to achieve the objectives of the inspection
- Ensure that Managers and Operators of a GMM activity are aware of their obligations in terms of availing their premises, facilities, documents, data and information for inspection when required by inspectors. Inspectors can make information requests in writing and may require the submission in the same manner as deemed necessary.
- Ensure that Managers and Operators of a GMM activity are responsible for ensuring that there is adequate preparation for the inspection, cooperation with the inspector and appropriate follow-up actions.



Outcomes of Compliance Monitoring and Inspection

No Breach of Regulatory Provisions

If there is no breach of the terms of the approval permit, institutional or national regulators, as appropriate, should allow the activity of GMM to continue without requiring adjustments to mitigate or manage risks. Finding no breach of the regulatory provisions is the expected outcome of a well-managed compliance program.

Minor Breach of Regulatory Provisions

In the event that the designated regulator observes a minor breach of the terms of approval of a GMM activity, the IBC should act to enforce the correction of the breaches and instruct the PI to make the required adjustments for the work to continue as approved. The IBC should notify the management of the institution and the NCA of the minor breaches and the corrective action that is taken.

Significant Breach of Regulatory Provisions

In a case where a breach of significant concern has been identified or suspected, the IBC or the NCA may order the redressing of the breaches and /or the suspension of the GMM activity. In a case where the breach is noted by the IBC, the IBC should notify, in writing, the NCA in accordance with the IBC guidelines. Depending on the severity of the case, the NCA in the jurisdiction may decide to sanction an investigation on the incident.

- In the event that there are significant breaches identified, the NCA within its powers can order for cessations of the work until improvement orders are addressed.
- When the NCA suspects breach incident was caused by negligence, they may decide to take legal action to make sure that the legal and regulatory provisions of the regulatory laws and regulations are enforced.

Classification of “Minor” and “Significant” Breach

For purposes of sub-sections 5.2 and 5.3 above, besides the exercise of good judgment at all times by the regulator, there shall be maintained a practice manual to provide categories of “minor breach” and “significant breach” at all levels of GMM activity.

Notification by Principal Investigators

The PI should obtain prior approval from the IBC and the NCA in order to implement any changes to the protocol, facilities or personnel. In case of an emergency situation, the PI should refer to the IBC Guidelines.

The PI shall notify in due time to the IBC and the NCA, any omission such as breach of the containment or confinement facility or possible unauthorised release or escape of the GMM in a laboratory study, population cage, CFT, or in transport. Corresponding mitigation measures undertaken shall also be notified.

Reporting

The IBC should submit progress reports and incident reports to the NCA as indicated in the Guidelines on Institutional Biosafety Committees.

Upon conducting an inspection, the inspector(s) shall produce the Inspection Report(s) and share a copy with the PI. Where there are corrective actions to be taken on the site arising from the inspection, both the PI and the inspector(s) will sign the report on-site to have the corrective actions implemented. In case there is lack of consensus or disagreement regarding outcomes of the Inspection Report, this should be noted in the report. A copy of the report will be sent to the IBC for its records.

Enforcement

Compliance monitoring or inspection entails enforcement plans (actions and timeframes) to correct breaches of the terms and conditions of the permits observed by the IBC. Likewise, inspection by the NCA can result in enforcement measures of various degrees, such as correcting lapses or, in extreme cases, measures to stop GMM activities. The latter will apply where breaches cannot be remedied.

Enforcement measures by IBC

The IBC should ensure that the PI addresses minor regulatory non-compliances noticed by providing remedial measures and that compliance standards are maintained as per the terms and conditions of approval of a GMM activity.

Enforcement measures by NCA

When non-compliances are substantial, meriting the attention of the NCA, the NCA, in coordination with the IBC and the PI, should have the duty to ensure that timely and adequate actions are taken to fix shortcomings in a GMM activity so that the required regulatory standard is met.

Communication

Planning and implementation of communication of the process and outcomes of compliance monitoring and inspection of activities involving GMM are critical to ensure transparency, predictability and accountability.

Communication duties of Biosafety Officer

The IBC should relay information about outcomes of compliance monitoring undertakings to GMM activity managers and implementers such as project PIs, Trial Managers and Facility Operators.

Communication Duties of NCA

The NCA should communicate the outcomes of its inspection on a GMM activity to the IBC, PI, Trial Managers and/or Facility Operators.

The NCA may also communicate the outcomes of its inspection on a GMM activity to the public in an appropriate manner that ensures confidence by the public in the regulatory body that all activities on GMM are undertaken in compliance with the terms of approval so as to manage potential risks to the minimum possible level.

Medium of Communication

Communication of business amongst parties involved will be held to a higher standard than everyday communication. The medium of communication will range from written (hard copy print or digital formats) to oral or spoken, electronic and multimedia. Platforms including but not limited to Website, Twitter and Facebook, shall be maintained for purposes of channelling information as deemed fit by the agencies.

Conclusion

This guideline on CMI is designed to ensure that regulatory work is not only conducted professionally but also bears a high level of credibility whilst maintaining the required accountability to the public. The guideline covers operations under the different phases of GMM development from the laboratory setting to cage population, confined field trials and full-scale deployment. This guideline seeks to facilitate the safe application of GMM as a steward by existing regulatory frameworks under the IBC and NCA.

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