

**PANDEMIC INFLUENZA PREPAREDNESS FRAMEWORK¹
FOR THE SHARING OF INFLUENZA VIRUSES AND
ACCESS TO VACCINES AND OTHER BENEFITS**

1. PRINCIPLES.....	4
2. OBJECTIVE.....	5
3. SCOPE	6
4. DEFINITIONS AND USE OF TERMS	6
4.1 Pandemic Influenza Preparedness Biological Materials or PIP Biological Materials	6
4.2 Other technical terms	6
4.3 Institutions, organizations and entities.....	7
4.4 Other terms	8
5. PANDEMIC INFLUENZA PREPAREDNESS SYSTEM FOR SHARING OF H5N1 AND OTHER INFLUENZA VIRUSES WITH HUMAN PANDEMIC POTENTIAL	9
5.1 General.....	9
5.2 Genetic sequence data.....	10
5.3 Traceability and reporting mechanisms	10
5.4 Standard Material Transfer Agreement	10
6. PANDEMIC INFLUENZA PREPAREDNESS BENEFIT SHARING SYSTEM	11
6.1 General.....	11
6.1 bis WHO Coordination of Pandemic Preparedness and Response	11
6.2 Pandemic risk assessment and risk response	11
6.3 Provision of PIP Candidate Vaccine Viruses.....	12
6.4 Provision of diagnostic reagents and test kits.....	12
6.5 Provision of reference reagents for potency determination of vaccines	12
6.6 Laboratory and influenza surveillance capacity building	13
6.7 Regulatory capacity building	13

¹ A proposal has been made for the use of the term “Guidelines” in place of “Framework” throughout this text. Proposals have also been made for the use of the terms “Multilateral Framework” or “International Framework” and/or “Global sharing”.

6.8	Antivirals stockpiles.....	13
6.9	Pandemic influenza preparedness vaccine stockpile.....	14
6.10	Access to vaccines in the inter-pandemic period for developing countries	14
6.11	Access to pandemic influenza vaccines	15
6.12	Tiered pricing.....	15
6.13	Technology transfer	15
6.14	Sustainable and innovative financing mechanisms	15
7.	GOVERNANCE AND REVIEW	17
7.1	General.....	17
7.2	Advisory Group.....	17
7.3	Governance and review of Terms of Reference for WHO GISRS Laboratories	18
7.4	Monitoring and review of the Framework	18
ANNEX 1	Standard Material Transfer Agreement 1	20
ANNEX 2	Standard Material Transfer Agreement 2	24
ANNEX 3	Advisory Group Terms of Reference	29
ANNEX 4	Guiding Principles for the development of Terms of Reference for current and potential future WHO GISRS Laboratories for H5N1 and other human pandemic influenza viruses.....	31
ANNEX 5	Terms of Reference related to work with Pandemic influenza preparedness biological materials for WHO GISRS Laboratories.....	32

1. PRINCIPLES

In relation to Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and Other Benefits, WHO Member States: (*Consensus*)

(PP1) Recall World Health Assembly resolution WHA60.28 on Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits; (*Consensus*)

(PP2) Note the continuing risk of an influenza pandemic with potentially devastating health, economic and social impacts, particularly for developing countries which suffer a higher disease burden and are more vulnerable; (*Consensus*)

(PP3) Recognize that Member States have a commitment to share on an equal footing H5N1 and other influenza viruses of human pandemic potential and the benefits, considering these as equally important parts of the collective action for global public health; (*Consensus*)

(PP4) This Framework will be guided by the goal of its universal application for the protection of all people of the world from the international spread of disease; (*Consensus*)

(PP5) Recall the need for rapid, systematic and timely sharing of H5N1 and other influenza viruses with human pandemic potential with WHO Collaborating Centres on Influenza and WHO H5 Reference Laboratories as a contribution to assessment of pandemic risk, development of pandemic vaccines, updating of diagnostic reagents and test kits, and surveillance for resistance to antiviral medicines; (*Consensus*)

(PP6) Reaffirm obligations of States Parties under the International Health Regulations (2005);¹ (*Consensus*)

(PP7) Recognize this Framework is to be implemented in a manner consistent with applicable national and international laws, regulations, and obligations; (*Consensus*)

(PP8) Recognize that the benefits arising from the sharing of H5N1 and other influenza viruses with human pandemic potential should be shared with all Member States based on public health risk and need; (*Consensus*)

(PP9) Recognize the need for a fair, transparent, equitable and efficient framework for the sharing of H5N1 and other influenza viruses with human pandemic potential and for the sharing of benefits, including access to and distribution of affordable diagnostics and treatments, including vaccines, to those in need, especially in developing countries, in a timely manner; (*Consensus*)

(PP10) Recognize also the WHO leadership and oversight functions over these issues and the need for collaboration with United Nations System Influenza Coordinator and relevant intergovernmental organizations; (*Consensus*)

(PP11) Recognizing the sovereign right of States over their biological resources and the importance of collective action to mitigate public health risks; (*Consensus*)

¹ See <http://www.who.int/csr/ihp/en/>.

(PP12) Recalling the Global Strategy on Public Health, Innovation and Intellectual Property, adopted in resolution WHA61.21 (*Consensus*)

(PP13) Recall that resolutions WHA60.28 and WHA61.21 recognize that “intellectual property rights do not and should not prevent Member States from taking measures to protect public health” and “that intellectual property rights are an important incentive in the development of new health care products. However, this incentive alone does not meet the need for the development of new products to fight diseases where the potential paying market is small or uncertain”; (*Consensus*)

(PP14) Recognize that the commitment to share on an equal footing H5N1 and other influenza viruses of human pandemic potential and the benefits enables WHO Member States and the Director-General to assess the global risk of an influenza pandemic and allows WHO Member States and the Director-General to take actions to reduce the risk of the emergence of a pandemic and to facilitate the development and production of vaccines, diagnostic materials and other pharmaceuticals that can assist in rapidly responding to and containing an emerging pandemic; (*Consensus*)

(PP15) Acknowledge with serious concern that current global influenza vaccine production capacity remains insufficient to meet anticipated need in a pandemic; (*Consensus*)

(PP16) Acknowledge with serious concern that the distribution of influenza vaccine manufacturing facilities is inadequate particularly in developing countries and that some Member States can neither develop, produce, afford nor access the vaccines and other benefits; (*Consensus*)

(PP17) Note the WHO Global pandemic influenza action plan to increase vaccine supply (GAP)¹ and its goal of reducing the gap between potential vaccine demand and supply during an influenza pandemic, by expanding the global capacity to produce influenza vaccine, including in developing countries; (*Consensus*)

(PP18) Recognize the importance of Member States, pharmaceutical manufacturers and other entities with access to relevant technologies in respect of influenza vaccine, diagnostics, and pharmaceuticals making specific efforts to transfer these technologies, skills, knowledge and know-how to countries, particularly developing countries, that do not currently have access to these technologies, skills, knowledge and know-how; (*Consensus*)

(PP 19) Recognize the need for financing mechanisms that would promote affordability and equitable access to quality influenza vaccines, medicines and technologies by developing countries. (*Consensus*)

2. OBJECTIVE

2.1 The objective of the Pandemic Influenza Preparedness Framework is to improve pandemic influenza preparedness and response, and strengthen the protection against the pandemic influenza by improving and strengthening the WHO global influenza surveillance and response system ("WHO GISRS"), with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing; (*Consensus*)

(i) the sharing of H5N1 and other influenza viruses with human pandemic potential; and (*Consensus*)

(ii) Access to vaccines and sharing of other benefits. (*Consensus*)

¹ Document WHO/CDS/EPR/GIP/2006.1;
http://www.who.int/csr/resources/publications/influenza/CDS_EPR_GIP_2006_1.pdf.

3. SCOPE

3.1 This Framework applies to the sharing of H5N1 and other influenza viruses with human pandemic potential and the sharing of benefits. *(Consensus)*

3.2 This Framework does not apply to seasonal influenza viruses or other non-influenza pathogens or biological substances that may be contained in clinical specimens shared under this Framework. *(Consensus)*

4. DEFINITIONS AND USE OF TERMS

For the purpose of this Framework, the following terms have the meanings assigned to them below. *(Consensus)*

4.1 Pandemic Influenza Preparedness Biological Materials or PIP Biological Materials

“PIP Biological Materials¹”, for the purposes of this Framework (and its annexed Standard Material Transfer Agreements (SMTAs) and Terms of Reference (TORs)) and the Influenza Virus Tracking Mechanism (IVTM), includes human clinical specimens,² virus isolates of wild type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from H5N1 and/or other influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth re-assortment. *(Consensus)*

Also included in "PIP Biological Materials" are RNA extracted from wild-type H5N1 and other human influenza viruses with human pandemic potential and cDNA that encompass the entire coding region of one or more viral genes.¹ *(Consensus)*

4.2 Other technical terms

“Genetic sequences” means the order of nucleotides found in a molecule of DNA or RNA. They contain the genetic information that determines the biological characteristics of an organism or a virus. *(Consensus)*

“Reference reagents” are biological or chemical substances or organisms and parts thereof used in diagnostic or surveillance activities. They are rigorously characterized and shown to be suitable for use as standards in order to compare and validate results of analyses obtained in different laboratories. *(Consensus)*

¹ OPERATIONAL EXEMPTION: materials shared within the WHO GISRS or with other laboratories specifically for non-commercial public health uses including surveillance activities, diagnostic applications, and quality assurance, are not handled as PIP Biological Materials. Their onward transfer for purposes other than those specified in the terms of reference of National Influenza Centers, WHO Collaborating Centres, Essential Regulatory Laboratories and H5 Reference Laboratories is not allowed under this operational exemption. *(Consensus)*

² The definition for this term has been provided. *(Consensus)*

“Reference reagents for potency determination of vaccines/vaccine potency reagents” means reagents used by vaccine manufacturers and regulatory laboratories for the purpose of testing and standardizing the potency of vaccines against H5N1 and other influenza viruses with human pandemic potential. (*Consensus*)

“Influenza virus with human pandemic potential” designates any wild-type influenza virus that has been found to infect humans and that has a haemagglutinin antigen that is distinct from those in seasonal influenza viruses so as to indicate that the virus has potential to be associated with pandemic spread within human populations with reference to the International Health Regulations (2005) for defining characteristics. (*Consensus*)

“Pandemic Influenza Preparedness vaccine virus” or “PIP vaccine virus” connotes any high-growth reassortant virus or any influenza reference virus, WHO-recommended influenza virus for vaccine use or other influenza virus material generated, including by new and emerging technologies, from H5N1 or other influenza virus with human pandemic potential that is provided to influenza vaccine manufacturers for the purposes of developing a prototype pandemic, pre-pandemic, pandemic or other influenza vaccine. (*Consensus*)

“Clinical specimens” means materials taken from humans or animals, in as far as the samples taken from animals are shared by originating countries/laboratories with the WHO GISRS. These include specimens collected from the respiratory tract (for example, swabs and aspirated fluid), and also blood, serum, plasma, feces, and tissues, for diagnostic purposes, detection of pathogens and further characterization, study or analysis. (*Consensus*)

“High-growth reassortant influenza viruses” means hybrid influenza viruses, including recombinant viruses, that have been generated from two or more different influenza viruses and selected to grow better in eggs or tissue cultures for optimal influenza vaccine production. (*Consensus*)

“Influenza reference viruses” means wild-type influenza viruses of human or animal origin that WHO has selected as representative of important groups of influenza viruses on the basis of extensive antigenic and genetic studies and comparisons with influenza viruses from many countries. As the influenza viruses evolve in nature, new influenza reference viruses are selected. (*Consensus*)

“WHO-recommended influenza viruses for vaccine use” means wild-type influenza viruses that are recommended by WHO as the basis for an influenza vaccine. (*Consensus*)

“Wild-type influenza viruses or influenza virus isolates” means naturally occurring influenza viruses that have been detected by any means including molecular methodology and/or cultured either in eggs or cells (i.e. isolated) directly from clinical specimens or subsequent culture passages and have not been purposefully modified. (*Consensus*)

4.3 Institutions, organizations and entities

“Essential regulatory laboratories” means influenza laboratories designated by WHO located in, or associated with, national regulatory agencies and which have a critical role at the global level for developing, regulating and standardizing human influenza vaccines. Such laboratories participate in the WHO GISRS in accordance with their corresponding terms of reference. (*Consensus*)

“Influenza vaccine, diagnostic and pharmaceutical manufacturers” means public or private entities including academic institutions, government owned or government subsidized entities, nonprofit organizations or commercial entities that develop and/or produce human influenza vaccines and other products derived from or using H5N1 or other influenza viruses of human pandemic potential. (*Consensus*)

“National Influenza Centres” or “NICs” means influenza laboratories authorized and designated by the Member State and subsequently recognized by WHO to perform a number of functions including

providing PIP Biological Materials to the WHO GISRS in accordance with the Terms of Reference. *(Consensus)*

“Other authorized laboratory” means influenza laboratories authorized by the Member State to provide PIP Biological Materials to the WHO GISRS. This term is intended to cover laboratories in those Member States which do not have a National Influenza Centre or Member States with NICs but which also have additional laboratories with certain roles usually performed by NICs. *(Consensus)*

“Public health researchers” means researchers in public health and/or basic sciences at public or private institutions outside of the WHO GISRS, universities and other academic research institutions with a primary research interest in public health. *(Consensus)*

“WHO Collaborating Centres on Influenza” or “WHO CCs” means influenza laboratories designated by WHO and supported by national authorities to perform certain roles within the WHO GISRS, and which have accepted formal Terms of Reference from WHO. In general, they differ from National Influenza Centres and WHO H5 Reference Laboratories in having global responsibilities and more extensive technical capacities. *(Consensus)*

“WHO H5 Reference Laboratories” means influenza laboratories that have been designated by WHO in order to strengthen national and regional capacity for reliably diagnosing H5 virus infection until this capacity is more widespread. *(Consensus)*

“WHO GISRS” means the international network of influenza laboratories, coordinated by WHO, that conduct year-round surveillance of influenza, assessing the risk of pandemic influenza and assisting in preparedness measures. The WHO GISRS comprises National Influenza Centres, WHO Collaborating Centres on Influenza, WHO H5 Reference Laboratories and Essential Regulatory Laboratories. *(Consensus)*

4.4 Other terms

“Advisory Group” means the Group referred to in section 7.2 of this Framework. *(Consensus)*

“Affected country” means countries with laboratory confirmed cases of H5N1, or other influenza viruses with human pandemic potential. *(Consensus)*

“Director-General” means the Director-General of the World Health Organization. *(Consensus)*

“Least-developed country” means those countries that are periodically classified as least-developed countries by the United Nations Committee for Development Policy. *(Consensus)*

“Originating laboratory” means a National Influenza Centre or other authorized laboratory that initially sends PIP Biological Materials/clinical specimens to other laboratories within the WHO GISRS and to other recipients. *(Consensus)*

“Originating Member State” means the Member State where the PIP Biological Materials/ clinical specimens were first collected. *(Consensus)*

“Pandemic Influenza Preparedness Framework” means this Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits. *(Consensus)*

“Influenza Virus Traceability Mechanism” (“IVTM”) means an IT based system for tracking the transfer and movement of PIP Biological Materials into, within and out of the WHO GISRS as defined in the Framework. (*Consensus*)

“WHO antivirals stockpile” means a reserved quantity of antiviral medicines and associated equipment for management of outbreaks of H5N1 and other influenza viruses with human pandemic potential, as specified in section 6.8 of this Framework. (*Consensus*)

“WHO Member States” means the States party to the WHO Constitution. (*Consensus*)

“WHO pandemic influenza preparedness vaccine stockpile” or “PIP vaccine stockpile” is the stockpile of vaccines for H5N1 or other influenza viruses with human pandemic potential referred to in section 6.9 of this Framework. (*Consensus*)

“WHO Secretariat” has the meaning assigned to it in the WHO Constitution. (*Consensus*)

5. PANDEMIC INFLUENZA PREPAREDNESS SYSTEM FOR SHARING OF H5N1 AND OTHER INFLUENZA VIRUSES WITH HUMAN PANDEMIC POTENTIAL

5.1 General

5.1.1 Member States, through their National Influenza Centres and Other authorized laboratories, should in a rapid, systematic and timely manner provide PIP Biological Materials from all cases of H5N1 and other influenza viruses with human pandemic potential, as feasible to the WHO Collaborating Centre on Influenza or WHO H5 Reference Laboratory of the originating Member State’s choice. (*Consensus*)

5.1.2 By providing PIP Biological Materials from National Influenza Centres and Other authorized laboratories to WHO Collaborating Centres on Influenza and WHO H5 Reference Laboratories as set out in section 5.1.1 above, Member States provide their consent for the onward transfer and use of PIP Biological Materials to institutions, organizations and entities, subject to provisions in the Standard Material Transfer Agreements. (*Consensus*)

5.1.3 National Influenza Centres and Other authorized laboratories will make, as feasible, efforts to ensure that PIP Biological Materials, from cases of H5N1 and other influenza viruses with human pandemic potential, that they provide to WHO Collaborating Centres on Influenza and WHO H5 Reference Laboratories: (*Consensus*)

- (i) contain viable material; (*Consensus*) and
- (ii) are accompanied by information as agreed in the Influenza Virus Traceability Mechanism and other clinical and epidemiological information needed for risk assessment. (*Consensus*)

5.1.4 Member States may also provide PIP Biological Materials directly to any other party or body on a bilateral basis provided that the same materials are provided on a priority basis to the WHO Collaborating Centres on Influenza and/or H5 Reference Laboratories under this Framework. (*Consensus*)

5.2 Genetic sequence data

5.2.1 Genetic sequence data, and analyses arising from that data, relating to H5N1 and other influenza viruses with human pandemic potential should be shared in a rapid, timely and systematic manner with the originating laboratory and among WHO GISRS laboratories. (*Consensus*)

5.2.2 Recognizing that greater transparency and access concerning influenza virus genetic sequence data is important to public health and there is a movement towards the use of public-domain or public-access databases such as Genbank and GISAID respectively; and (*Consensus*)

5.2.3 Recognizing that in some instances the publication of genetic sequence data has been considered sensitive by the country providing the virus; (*Consensus*)

5.2.4 Member States request the Director-General to consult the Advisory Group on the best process for further discussion and resolution of issues relating to the handling of genetic sequence data from H5N1 and other influenza viruses with pandemic potential as part of the Pandemic Influenza Preparedness Framework. (*Consensus*)

5.3 Traceability and reporting mechanisms

5.3.1 The Director-General, in consultation with the Advisory¹ Group, will put in place in a timely manner a transparent traceability mechanism that uses an electronic system in order to track in real time the movement of PIP Biological Materials into, within, and out of the WHO GISRS. (*Consensus*)

5.3.2 To ensure that rapid, systematic and timely feedback is provided to Originating laboratories and Member States, the Director-General will also include in the traceability mechanism and associated electronic reporting systems a request that WHO Collaborating Centres, H5 Reference Laboratories and Essential Regulatory Laboratories provide a summary report of laboratory analyses and on request any other available information required by the originating laboratory regarding PIP Biological Materials. (*Consensus*)

5.3.3 In order to ensure the IVTM does not hinder the functioning of the WHO GISRS during pandemic influenza emergencies, as determined by the Director-General, the Director-General may temporarily modify the requirement to record all PIP Biological Materials. Such a modification must be limited to the pandemic virus strain or strains connected with the emergency. (*Consensus*)

5.3.4 The Director General shall report on any such modification to Member States. (*Consensus*)

5.4 Standard Material Transfer Agreement¹

5.4.1 The Standard Material Transfer Agreement 1 (SMTA 1) in Annex 1 will be used to cover all transfers of PIP Biological Materials within the WHO GISRS for the duration of its applicability. (*Consensus*)

¹ At the November 2007 session of the IGM, the term “advisory mechanism” was substituted for the term “oversight mechanism” used in resolution WHA60.28.

5.4.2 The Director-General will, using the Standard Material Transfer Agreement 2 (SMTA 2) in Annex 2, enter into agreements with entities outside the WHO GISRS. Such agreements will cover all transfers of PIP Biological Materials to recipients for their duration. *(Consensus)*

6. PANDEMIC INFLUENZA PREPAREDNESS BENEFIT SHARING SYSTEM

6.1 General

6.1.1. Member States should, working with the WHO Secretariat, contribute to a pandemic influenza benefit-sharing system and call upon relevant institutions, organizations, and entities, influenza vaccines, diagnostics and pharmaceutical manufacturers and public health researchers to also make appropriate contribution to this system. *(Consensus)*

6.1.2 The PIP Benefit Sharing System will operate to:

(i) provide pandemic surveillance and risk assessment and early warning information and services to all countries; *(Consensus)*

(ii) provide benefits, including, where appropriate, capacity building in pandemic surveillance, risk assessment, and early warning information and services to Member States. *(Consensus)*

(iii) prioritize important benefits, such as and including antiviral medicines and vaccines against H5N1 and other influenza viruses with human pandemic potential as high priorities, to developing countries, particularly affected countries, according to public health risk and needs and particularly where those countries do not have their own capacity to produce or access influenza vaccines, diagnostics and pharmaceuticals. Prioritization will be based on assessment of public health risk and need, by experts with transparent guidelines; *(Consensus)*

(iv) build capacity in receiving countries over time for and through technical assistance and transfer of technology, skills and know-how and expanded influenza vaccine production, tailored to their public health risk and needs. *(Consensus)*

6.1.3 The Pandemic Influenza Preparedness Benefit Sharing System will include the elements set out in the remainder of this part. *(Consensus)*

6.1 bis WHO Coordination of Pandemic Preparedness and Response

WHO will coordinate influenza pandemic preparedness and response in accordance with applicable IHR provisions and this Framework. As regards to the benefits outlined in this Framework, WHO should pay particular attention to policies and practices to promote the fair, equitable and transparent allocation of scarce medical resources (including, but not limited to, vaccines, anti-virals and diagnostic materials) during pandemics based on public health risk and needs, including the epidemiology of the pandemic. During inter-pandemic periods, WHO will work with Member States and relevant stakeholders to prepare for the aforementioned role. *(Consensus)*

6.2 Pandemic risk assessment and risk response

6.2.1 WHO GISRS laboratories will make available to the WHO Secretariat and the originating Member State, in a rapid, systematic and timely manner, a summary report of laboratory analyses and on request any other available information required regarding PIP Biological Materials to enable the

affected countries and in particular, developing countries, an effective and meaningful risk response. *(Consensus)*

6.2.2 WHO will provide information on risk response including, but not limited to, information on development of vaccines, candidate virus and effective antivirals to all affected countries and in particular, to developing countries, to enable an effective and meaningful risk response. *(Consensus)*

6.2.3 The WHO Secretariat will make available to all Member States, in a rapid, systematic and timely way, pandemic risk assessments and assist with risk response with all necessary supporting information. *(Consensus)*

6.2.4 WHO Collaborating Centres on Influenza and WHO H5 Reference Laboratories and the Director-General will actively continue to provide technical assistance to Member States to enhance research and surveillance capacity, including staff training, with the objective of improving national pandemic risk assessment and pandemic risk response. *(Consensus)*

6.3 Provision of PIP Candidate Vaccine Viruses

6.3. The Director-General will ensure that WHO Collaborating Centres on Influenza/H5 Reference Labs and Essential Regulatory Laboratories, as agreed in the Terms of Reference, provide PIP candidate vaccine viruses upon request: *(Consensus)*

- (i) to influenza vaccine manufacturers on a no preference basis; *(Consensus)*
- (ii) at the same time to the laboratories of originating and other Member States; *(Consensus)*
- (iii) to any other laboratory. *(Consensus)*

6.3bis Any entity receiving PIP candidate vaccine viruses will meet appropriate biosafety guidelines (*WHO Laboratory Biosafety Manual*, 3rd edition) and employ laboratory protection best practices. *(Consensus)*

6.4 Provision of diagnostic reagents and test kits

6.4.1 WHO Collaborating Centres on Influenza, WHO H5 Reference Laboratories and Essential Regulatory Laboratories, working with the WHO Secretariat, will continue to make available to National Influenza Centres and Other authorized laboratories, without charge, supplies of noncommercial diagnostic reagents and test kits for the identification and characterization of clinical specimens of influenza. *(Consensus)*

6.4.2 Influenza diagnostic manufacturers receiving PIP Biological Materials are urged to make available to WHO GISRS laboratories, without charge or at concessional and/or preferential rates, supplies of diagnostic reagents and test kits for the identification and characterization of clinical specimens of influenza, if circumstances warrant. *(Consensus)*

6.5 Provision of reference reagents for potency determination of vaccines

6.5.1 Essential regulatory laboratories (ERLs) will continue to provide, upon request, reference reagents for potency determination of vaccines against H5N1 and other viruses of human pandemic

potential to national regulatory laboratories and influenza vaccine manufacturers of all Member States. *(Consensus)*

6.5.2 ERLs will continue to provide upon request, training in quality control of vaccines against H5N1 and other viruses of human pandemic potential to national regulatory laboratories of all Member States. *(Consensus)*

6.6 Laboratory and influenza surveillance capacity building

6.6.1 Upon request, Member States with advanced laboratory and influenza surveillance capacity are urged to continue to work with WHO and other Member States, particularly developing countries to develop national laboratory and influenza surveillance capacity, including: *(Consensus)*

- (i) to conduct early detection, isolation and characterization of viruses; *(Consensus)*
- (ii) to participate in pandemic risk assessment and response; *(Consensus)*
- (iii) to develop research capacity related to influenza; *(Consensus)*
- (iv) to achieve technical qualifications for consideration of laboratories as National Influenza Centres, WHO H5 Reference Laboratories and WHO Collaborating Centres on Influenza. *(Consensus)*

6.7 Regulatory capacity building

6.7.1 Upon request, Member States with advanced regulatory capacity should improve and strengthen the work that has been undertaken by Member States with WHO, particularly developing countries to strengthen the capacity of regulatory authorities to carry out the necessary measures for the rapid approval of safe and effective human influenza vaccines, diagnostics and pharmaceutical products, including products developed from the use of PIP Biological Materials, especially those derived from new sub-types of influenza viruses. *(Consensus)*

6.7.2 Member States should make publicly available information on the notification of health regulatory approval of vaccines, diagnostics and pharmaceutical products for H5N1 and other influenza viruses with human pandemic potential, including those developed from the use of PIP Biological Materials. *(Consensus)*

6.8 Antivirals stockpiles

6.8.1 The Director-General will continue to work with other multilateral agencies, donors, international philanthropic organizations/entities, private foundations, and other potential partners, including institutions, organizations and entities and in particular influenza vaccine, diagnostic and pharmaceutical manufacturers, to seek commitments for contributions, maintain and further develop a stockpile of antiviral medicines and associated equipment for use in containment of outbreaks of H5N1 and other influenza viruses with human pandemic potential. *(Consensus)*

6.8.2 The Director-General will continue to coordinate with Member States, institutions, organizations and other entities and encourage them to maintain and further develop stockpiles of antiviral medicines and associated equipment for use in containment of outbreaks of H5N1 and other influenza viruses with human pandemic potential. *(Consensus)*

6.8.3 The Director-General will continue to seek the guidance of expert advice in determining the size, composition, replenishment, operational use and deployment procedures for use of the WHO antivirals stockpile. *(Consensus)*

6.9 Pandemic influenza preparedness vaccine stockpile

6.9.1 The Director-General will establish and maintain a stockpile of vaccines for H5N1 and other influenza viruses with human pandemic potential and associated equipment, including syringes, needles and applicators, consistent with expert guidance. *(Consensus)*

6.9.2 The WHO stockpile will initially include 150 million doses of H5N1 vaccine for use in accordance with expert guidance including SAGE. Indicatively: *(Consensus)*

(i) 50 million doses will be for use in affected countries, according to public health risk and need, to assist in containing the first outbreak or outbreaks of an emerging pandemic; and *(Consensus)*

(ii) 100 million doses will be for distribution, once a pandemic begins, to developing countries that have no or inadequate access to H5N1 influenza vaccines, on a per capita basis, with use to be determined by those countries. *(Consensus)*

6.9.3 Member States should urge influenza vaccine manufacturers to prioritize and respond to the needs of the WHO PIP vaccine stockpile and to donate sufficient doses of vaccines for H5N1 to meet its initial target (see 6.9.1 above). *(Consensus)*

6.9.4 The Director-General will continue to seek the guidance of experts in determining the size, composition, replenishment and operational use of the vaccines in the WHO PIP vaccine stockpile for H5N1 and other influenza viruses with human pandemic potential. *(Consensus)*

6.9.5 If insufficient doses are donated, the Director-General will work with Member States to explore the use of sustainable financing mechanisms (see 6.14 below) to meet the requirements of the WHO PIP vaccine stockpile. *(Consensus)*

6.9.5bis The Director-General will, with the guidance of experts, keep under review the potential for the pre-pandemic use of the WHO PIP vaccine stockpile in affected countries, including by supporting trials as appropriate. *(Consensus)*

6.9.6 The Director-General will work with relevant experts and Member States to develop and exercise operational plans for the deployment of the vaccines in the WHO PIP vaccine stockpile. *(Consensus)*

6.10 Access to vaccines in the inter-pandemic period for developing countries

6.10.1 Separately from measures to support the WHO PIP vaccine stockpile set out at section 6.9 above: *(Consensus)*

(i) Member States should urge influenza vaccine manufacturers to set aside a portion of each production cycle of vaccines for H5N1 and other influenza viruses with human pandemic potential for stockpiling and/or use, as appropriate, by developing countries; and *(Consensus)*

(ii) Member States should continue to work with each other, with the Director-General and with influenza vaccine manufacturers, with the aim of ensuring that adequate quantities of vaccines for H5N1 and other influenza viruses with human pandemic potential are made available to developing countries at the same time as to developed countries, on the basis of public health risk and needs and at tiered prices (see 6.12 below). *(Consensus)*

6.11 Access to pandemic influenza vaccines

6.11.1 Member States should urge vaccine manufacturers to set aside a portion of each production cycle of pandemic influenza vaccine for use by developing countries; and *(Consensus)*

6.11.2 The Director-General, consulting Member States and the Advisory Group, will convene an expert group to continue to develop international mechanisms, including existing ones, for the production and distribution of influenza vaccines on the basis of public health risk and needs during a pandemic, for consideration by the World Health Assembly in 2010. *(Consensus)*

6.12 Tiered pricing

As a measure to improve the affordability for developing countries of pandemic influenza vaccines and vaccines for H5N1 and other influenza viruses with human pandemic potential, and antivirals, Member States should urge influenza vaccine and antiviral manufacturers individually to implement tiered pricing for these vaccines and antivirals. As part of this approach, influenza vaccine and antiviral manufacturers individually should be urged to consider the income level of the country, and negotiate with the national authorities, of the recipient country in arriving at the price to be applied in the private and public markets of each country. In this context the vulnerability of the least developed countries should be taken into account. *(Consensus)*

6.13 Technology transfer

6.13.1 The Director-General will continue to work closely with Member States and influenza vaccine manufacturers to implement the WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply, including its strategies to build new production facilities in developing and/or industrialized countries and through transfer of technology, skills and know-how. *(Consensus)*

6.13.2 Member States should urge influenza vaccine, diagnostic and pharmaceutical manufacturers to make specific efforts to transfer these technologies to other countries, particularly developing countries, as appropriate. *(Consensus)*

6.13.3 Technology transfer should be conducted in a manner consistent with applicable national laws and international laws and obligations, facilitated progressively over time, on mutually agreed terms, and be suitable to the capacity of recipient Member States, to empower developing countries to study and manufacture influenza vaccines, diagnostics and pharmaceuticals. *(Consensus)*

6.13.4 Influenza vaccine manufacturers who receive PIP Biological Materials may grant, subject to any existing licensing restrictions, on mutually agreed terms, a non-exclusive, royalty-free licence to any influenza vaccine manufacturer from a developing country, to use its intellectual property and other protected substances, products, technology, know-how, information and knowledge used in the process of influenza vaccine development and production, in particular for pre-pandemic and pandemic vaccines for use in agreed developing countries. *(Consensus)*

6.13.5 Member States seeking to receive technology to produce influenza vaccine should be encouraged to first conduct studies on the disease burden of seasonal influenza with related economic analysis in their country. Should the study warrant, Member States should be encouraged to consider incorporating seasonal influenza vaccination into their national immunization programme, which will enable sustainable functioning of the manufacturing facilities. *(Consensus)*

6.14 Sustainable and innovative financing mechanisms

6.14.1 With a view to ensuring the sustainable financing of the PIP Benefit Sharing System, particularly for developing countries; and *(Consensus)*

6.14.2 Having regard to the desirability of all Member States and recipients of PIP Biological Materials contributing to the PIP Benefit Sharing System, financially or in kind, according to their capacity and over time; *(Consensus)*

6.14.3 Influenza vaccine, diagnostic and pharmaceutical manufacturers, using the WHO GISRS will make an annual partnership contribution to WHO for improving global pandemic influenza preparedness and response. It is decided that the sum of the annual contributions shall be equivalent to 50% of the running costs of the WHO GISRS¹. Such contributions will commence in 2012. The distribution between companies is to be based on transparency and equity, based on their nature and capacities. The Director-General in consultation with the "Advisory Group" will further define the specific amounts to be contributed by each company as well as the mechanism for implementation (see section 6.14.5 below). In so doing, the Director General and the "Advisory Group" will collaborate with industry. The Director General will report annually on the outcome to the Executive Board. *(Consensus)*

6.14.3.1 Member States and other stakeholders are encouraged to consider making donations and in-kind contributions to WHO for improving global pandemic influenza preparedness and response. *(Consensus)*

6.14.4 The contribution acquired under 6.14.3 shall be used for improving pandemic preparedness and response, inter alia for conducting disease burden studies, strengthening laboratory and surveillance capacity, access and effective deployment of pandemic vaccines and antiviral medicines. *(Consensus)*

6.14.5 The Director-General will propose to the EB which proportion of contributions should be used for inter-pandemic preparedness measures, and which proportion should be reserved for response activities in the event of a pandemic, based on advice of the "Advisory Group." *(Consensus)*

6.14.6 The Director-General based on advice from the "Advisory Group" will decide on the use of resources. The Director-General and the "Advisory Group" will interact with manufacturers and other stakeholders. *(Consensus)*

6.14.7 Member States are urged to continue to support the speedy and successful implementation of the WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply by 2015 by providing adequate financial support in accordance with Framework section 6.13.1 and 6.13.2. *(Consensus)*

6.14.8 Member States are urged to support the availability and rapid expansion of the safe use of adjuvant technology through WHO as appropriate while at the same time strengthening the monitoring of vaccine safety. *(Consensus)*

6.14.9 Member States are urged to continue and increase their support to strengthen laboratory and surveillance capacity particularly in developing countries by providing adequate financial and technical support in accordance with Framework section 6.6. *(Consensus)*

¹ The running costs of the GISRS for 2010 was approximately USD 56.5 million. The running costs of the WHO GISRS are understood to be a reference index for the partnership contribution of 50%. Such running costs may change over time and the partnership contribution will change accordingly. Such running costs are not to include the partnership contribution themselves.

7. GOVERNANCE AND REVIEW

7.1 General

7.1.1 The implementation of this Framework will be overseen by the World Health Assembly with advice from the Director-General. (*Consensus*)

7.1.2 An oversight mechanism is hereby established, which includes the World Health Assembly, the Director-General and the independent “Advisory Group”, established in connection with the Interim Statement of November 2007, and composed of international experts serving the Organization exclusively. Respectively, their function will be as follows: (*Consensus*)

(i) The Health Assembly, consistent with the Organization’s Constitutional function to act as the “directing and co-ordinating” authority on international health work, as set forth in Article 2(a) of the WHO Constitution, will oversee implementation of the Framework. (*Consensus*)

(ii) The Director-General, consistent with her role and responsibilities, particularly in connection with Collaborating Institutions and Other Mechanisms of Collaboration, inter alia, will promote implementation of the Framework within WHO and among relevant WHO-related entities. (*Consensus*)

(iii) In order that the Health Assembly and Director-General have appropriate expert monitoring and evaluation processes to support these functions, the Advisory Group, as provided for in this section, will provide evidence-based reporting, assessment and recommendations regarding the functioning of the Framework. The Advisory Group, consistent with WHO practice regarding such independent expert bodies, will advise the Director-General but will not itself engage in administrative functions, such as the recognition, or withdrawal of recognition, of technical institutions, nor will it have a public role, except as authorized. (*Consensus*)

7.2 Advisory Group

7.2.1 The Director-General will maintain the Advisory Group, referenced in section 7.1.2 above, to monitor and provide guidance to strengthen the functioning of the WHO GISRS and undertake necessary assessment of the trust-based system needed to protect public health and to help ensure implementation of this Framework. (*Consensus*)

7.2.2 The Director-General, in consultation with Member States, will continue to ensure that the Advisory Group is based on equitable representation of the WHO regions and of affected countries, taking into account balanced representation between developed and developing countries. (*Consensus*)

7.2.3 The Advisory Group will comprise 18 members drawn from three Member States in each WHO Region, with a skill mix of internationally recognized policy makers, public health experts and technical experts in the field of influenza. (*Consensus*)

7.2.4 The Advisory Group will function to assist the Director-General in monitoring the implementation of this Framework, in accordance with the terms of reference for the Advisory Group at Attachment 2 to this Framework. (*Consensus*)

7.2.5 The Advisory Group will present an annual report to the Director-General on its evaluation of the implementation of this Framework. The report should cover the following:

- (i) necessary technical capacities of WHO GISRS
- (ii) operational functioning of WHO GISRS
- (iii) WHO GISRS influenza pandemic preparedness priorities, guidelines and best practices (e.g. vaccine stockpiles, capacity building)
- (iv) increasing and enhancing surveillance for H5N1 and other influenza viruses with human pandemic potential
- (v) the Influenza Virus Tracking Mechanism.
- (vi) the sharing of influenza viruses and access to vaccines and other benefits
- (vii) use of financial and non-financial contributions (*Consensus*)

7.2.6 The Director-General will present a report on the work carried out by the Advisory Group through the Executive Board to the Sixty- fifth World Health Assembly in 2012 for its consideration including a decision on the Advisory Group's future mandate. (*Consensus*)

7.3 Governance and review of Terms of Reference for WHO GISRS Laboratories

7.3.1 The Terms of Reference of the WHO Collaborating Centres on Influenza, WHO H5 Reference Laboratories, National Influenza Centres and Essential Regulatory Laboratories should be developed in accordance with the guiding principles outlined in Attachment 3 to this Framework. (*Consensus*)

7.3.2 The Director-General in consultation with the Advisory Group and competent authorities in Member States, and the WHO Collaborating Centres, WHO H5 Reference Laboratories, National Influenza Centres, and Essential Regulatory Laboratories will review periodically the Terms of Reference of the institutions and laboratories of the WHO GISRS and amend them when needed, to promote the principles provided by this Framework, and report thereon to the World Health Assembly. (*Consensus*)

7.3.3 Member States may bring to the attention of the Director-General allegations of non-compliance by institutions and laboratories of the WHO GISRS with their respective terms of reference or the Standard Material Transfer Agreements. (*Consensus*)

7.3.4 In the event of any alleged breaches of the Terms of Reference or the Standard Material Transfer Agreements by a WHO Collaborating Centre on Influenza, WHO H5 Reference Laboratories or National Influenza Centre, and Essential Regulatory Laboratories, the Director-General will review the circumstances and may discuss with the Advisory Group any appropriate action in response to those breaches. Where there has been a serious breach, the Director-General may consider suspending or revoking the WHO designation of the relevant laboratory. (*Consensus*)

7.4 Monitoring and review of the Framework

7.4.1 The Director-General, shall on a biennial basis inform the WHA, through the EB, on the status of, and progress on:

- (i) Laboratory and surveillance capacity (see Framework section 6.6)
- (ii) Global influenza vaccine production capacity (see Framework section 6.13.1 and 6.13.2)
- (iii) Status of agreements entered into with industry, including information on access to vaccines, antivirals and other pandemic material (6.14.3 and 6.14.4)
- (iv) Financial report on the use of the partnership contribution (6.14.5)
- (v) The experience arising from the use of the definition of PIP Biological Materials in Section 4.1 (*Consensus*)

7.4.2 The Framework and its Annexes will be reviewed by 2016 with a view to proposing revisions reflecting developments as appropriate, to the World Health Assembly in 2017, through the Executive Board. (*Consensus*)

ANNEX 1

SMTA 1

Standard Material Transfer Agreement within the WHO GISRS (SMTA 1)

In furtherance of the Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits (the “Framework”), this Standard Material Transfer Agreement (“Agreement” or “SMTA 1”) has been developed. *(Consensus)*

Article 1. Parties to the Agreement

1.1 Parties to SMTA 1 are limited to influenza laboratories that have been designated or recognized by WHO and have accepted to work under agreed WHO Terms of Reference. In this Agreement: *(Consensus)*

The Provider is the laboratory sending Materials, as herein defined,

(name and address of the provider or providing institution, designation of the laboratory (i.e. whether NIC/WHO CC/H5RL/ERL/other authorized laboratory), name of authorized official, contact information for authorized official) (hereinafter referred to as “the Provider”) *(Consensus)*

and

The Recipient is the laboratory receiving Materials, as herein defined, *(Consensus)*

(name and address of the recipient or recipient institution, designation of the laboratory (i.e. whether NIC/WHO CC/H5RL/ERL/other authorized laboratory), name of authorized official, contact information for authorized official) (hereinafter referred to as “the Recipient”) *(Consensus)*

1. 2 . Provider and Recipient are hereafter collectively referred to as “Parties”. *(Consensus)*

Article 2. Subject Matter of the Agreement

PIP Biological Materials as defined in Section 4.1 of the Framework (hereinafter “Materials”) transferred from the Provider to the Recipient are subject to the provisions of this Agreement. *(Consensus)*

Article 3. General Provisions

The Provider or recipient will consider to support the strengthening of the laboratory and surveillance capacity of the networks of developing countries. (*Consensus*)

Article 4. Rights and Obligations of the Provider

4.1 The Provider undertakes the following with respect to the Materials:

4.1.1. To comply with its respective WHO GISRS Terms of Reference. (*Consensus*)

4.1.2. To ensure that the Materials are handled in accordance with applicable WHO guidelines and national bio-safety standards.¹ (*Consensus*)

4.2. The Provider agrees to the onward transfer and use of the Materials, to all members of the WHO GISRS, on the same terms and conditions as those provided in SMTA 1. (*Consensus*)

4.3 The Provider consents to the onward transfer and use of the Materials to entities outside the WHO GISRS on the condition that the prospective recipient has concluded an SMTA 2. (*Consensus*)

4.4. The Provider shall inform the WHO of shipments of Materials to entities inside/outside the WHO GISRS by recording in the IVTM. (*Consensus*)

Article 5. Rights and obligations of the Recipient

5.1 The Recipient undertakes the following with respect to the Materials:

5.1.1 To comply with its respective WHO GISRS Terms of Reference. (*Consensus*)

5.1.2. To ensure that the Materials are handled in accordance with applicable WHO guidelines and national bio-safety standards. (*Consensus*)

5.1.3. To inform WHO of shipments of Materials to entities inside/outside the WHO GISRS by recording in the IVTM (*Consensus*)

5.1.4 In the event of further transfers within the WHO GISRS, to do so in accordance with SMTA 1. (*Consensus*)

5.2. The Recipient shall actively seek the participation of scientists to the fullest extent possible from originating laboratories and other authorized laboratories, especially those from developing countries, in scientific projects associated with research on clinical specimens and/or influenza virus from their countries and actively engage them in preparation of manuscripts for presentation and publication. (*Consensus*)

¹ “WHO Guidelines on Regulations for the Transport of Infectious Substances” and “WHO Guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection.”

5.3. The Recipient shall appropriately acknowledge in presentations and publications, the contributions of collaborators, including laboratories/countries providing clinical specimens or influenza virus with pandemic potential or reagents, using existing scientific guidelines. *(Consensus)*

Article 6. Intellectual Property Rights

6.1 Neither the Provider nor the Recipient should seek to obtain any intellectual property rights (IPRs) on the Materials. *(Consensus)*

6.2 The Provider and the Recipient acknowledge that any IPRs on the Materials obtained before the date of adoption of the Framework by the World Health Assembly will not be affected by SMTA 1. *(Consensus)*

6.3 The Provider under SMTA 1 may have used technology protected by IPRs for the generation and/or modification of the Materials. Any recipient of such Materials acknowledges that such IPRs shall be respected. *(Consensus)*

Article 7. Dispute Resolution

7.1. In the event of a dispute under SMTA 1, Parties concerned shall seek in the first instance to settle the dispute through negotiation or any other amicable means of their own choice. Failure to reach agreement shall not absolve the parties to the dispute from the responsibility of continuing to seek to resolve it. *(Consensus)*

7.2. In the event that the dispute is not settled by the means described under paragraph 1 of this Article, one of the Parties concerned may refer the dispute to the Director-General, who may seek advice of the Advisory Group with a view to settling it. The Director-General may make recommendations to the Parties regarding its resolution and shall report to the World Health Assembly on any such matters. *(Consensus)*

7.3. The Parties also acknowledge the role of the Director-General under the Framework, in particular 7.3.4. *(Consensus)*

Article 8. Warranty

The Provider makes no warranties as to the safety of the Materials, or as to the accuracy or correctness of any data provided with them. Likewise, the provider does not make any warranties as to the quality, viability, or purity (genetic or mechanical) of the Materials being furnished. The Provider and the Recipient assume full responsibility for complying with their respective national biosecurity and biosafety regulations and rules as to import, export or release of biological materials. *(Consensus)*

Article 9. Duration of Agreement

This contractual agreement shall remain in force until December 31, 2021 and shall be automatically renewed until December 31, 2031 unless the World Health Assembly decides otherwise. *(Consensus)*

Article 10. Acceptance and Applicability

10.1.1 Recipients or Providers in the WHO GISRS at the time of the adoption of the Framework by the World Health Assembly: Acceptance by such laboratories of their WHO Terms of Reference, as contained in the Framework, constitutes acceptance of SMTA 1. (*Consensus*)

10.1.2 Recipients or Providers that join the WHO GISRS after adoption of the Framework by the World Health Assembly: Acceptance of designation or recognition by WHO to become a WHO GISRS laboratory will constitute acceptance of SMTA 1. (*Consensus*)

10.2. Applicability: SMTA 1 shall cease to be applicable only upon suspension or revocation of designation or recognition by WHO or upon formal withdrawal by the laboratory of its participation in the WHO GISRS or upon mutual agreement of the WHO and the laboratory. Such a suspension, revocation or withdrawal shall not relieve a laboratory of pre-existing obligations under SMTA 1. (*Consensus*)

Article 11. Signature

Further to Article 10 above entitled "Acceptance & Applicability", unless either party requires this Agreement to be executed by signature of a printed document, no further evidence of acceptance is required. (*Consensus*)

ANNEX 2

SMTA 2

Standard Material Transfer Agreement outside WHO GISRS (SMTA 2)

Article 1. Parties to the Agreement

WHO and Recipient.¹ (*Consensus*)

Article 2. Subject Matter of the Agreement

PIP Biological Materials as defined in Section 4.1 of the Framework (hereinafter “Materials”) transferred to the Recipient are subject to the provisions of this Agreement. (*Consensus*)

Article 2. bis Definitions

(a) As provided for in Section 4 of the Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefit.

(b) Other terms as agreed by the parties.

Article 3. Obligations of the Provider

To be agreed by the parties. (*Consensus*)

Article 4. Obligations of the Recipient

4.1 The recipient agrees to comply with the commitments selected below, in accordance with the terms set out in the Annex to this agreement. (*Consensus*)

4.1.1 The recipient shall comply with the commitments selected on a timetable determined by the WHO in consultation with the Advisory Group established by the PIP Framework and in coordination with the recipient, based on optimal pandemic preparedness and response considerations. (*Consensus*)

¹ Recipients are all entities that receive “PIP Biological Materials” from the WHO GISRS, such as influenza vaccine, diagnostic and pharmaceutical manufacturers, as well as biotechnology firms, research institutions and academic institutions. Each recipient shall select options based on its nature and capacities.

A. For manufacturers of vaccines and/or antivirals, the recipient shall commit to at least two of the following options:

A1. Donate at least **10%**¹ of real time pandemic vaccine production to WHO
(*Consensus*)

A2. Reserve at least **10%**¹ of real time pandemic vaccine production at affordable prices to WHO (*Consensus*)

A3. Donate at least **X treatment courses** of needed antiviral medicine for the pandemic to WHO (*Consensus*)

A4. Reserve at least **X treatment courses** of needed antiviral medicine for the pandemic at affordable prices (*Consensus*)

A5. Grant to manufacturers in developing countries licenses on mutually agreed terms that should be fair and reasonable including in respect of affordable royalties, taking into account development levels in the country of end use of the products, on technology, know-how, products and processes for which it holds IPR for the production of (i) influenza vaccines, (ii) adjuvants, (iii) antivirals and/or (iv) diagnostics. (*Consensus*)

A6. Grant royalty free licenses to manufacturers in developing countries or grant to WHO royalty-free, non-exclusive licenses on IPR, which can be sublicensed, for the production of pandemic influenza vaccines, adjuvants, antivirals products and diagnostics needed in a pandemic. WHO may sublicense these licenses to manufacturers in developing countries on appropriate terms and conditions and in accordance with sound public health principles. (*Consensus*)

Where Option 5 or 6 is selected, the Recipient shall regularly provide to WHO information on granted licenses and the status of implementation of the licensing agreement. WHO shall provide such information to the Advisory Group.
(*Consensus*)

B. Manufacturers of products relevant to pandemic influenza preparedness and response, that are not manufacturing vaccines or antivirals, shall commit to one of the following options: A5, A6, and B1, B2, B3 and B4, as listed below.
(*Consensus*)

B1. Donate to WHO at least x^1 diagnostic kits needed for pandemics
(*Consensus*)

¹ Recognizing that flexibility is important in negotiating with all manufacturers, in a range of 5-20%

B2. Reserve for WHO at least x^3 diagnostic kits needed for pandemics, at affordable prices (*Consensus*)

B3. Support, in coordination with WHO, the strengthening of influenza specific laboratory and surveillance capacity in developing countries (*Consensus*)

B4. Support, in coordination with WHO, transfer of technology, know-how and/or processes for pandemic influenza preparedness and response in developing countries (*Consensus*)

C. The recipient shall, in addition to the commitments selected under A or B above, consider contributing to the measures listed below, as appropriate:

- Donations of vaccines
- Donations pre-pandemic vaccines
- Donations of antivirals
- Donations of medical devices
- Donations of diagnostic kits
- Affordable pricing
- Transfer of technology and processes
- Granting of sublicenses to WHO
- Laboratory and surveillance capacity building (*Consensus*)

4.2 The Recipient shall ensure that the PIP Biological Materials are handled in accordance with applicable WHO guidelines and national bio-safety standards. (*Consensus*)

4.3 If applicable, the Recipient shall appropriately acknowledge in presentations and publications, the contributions of WHO laboratories providing the materials identified in Article 2, using existing scientific guidelines. (*Consensus*)

4.4 The recipient shall only further transfer the PIP Biological Materials if the prospective recipient has concluded an SMTA with the World Health Organization. Any such further transfer shall be reported to the World Health Organization. The Director-General may, under exceptional circumstances, allow the PIP Biological Materials to be transferred to a prospective recipient while requesting this aforementioned recipient to enter into an SMTA, and report to the "Advisory Group" accordingly. (*Consensus*)

4.5 The recipient may exchange PIP Biological Materials with any other holder of an SMTA concluded with the World Health Organization (*Consensus*)

¹ Recognizing that flexibility is important in negotiating with all manufacturers

Article 5. Dispute Resolution

If a dispute cannot be resolved through negotiations or other non-binding means of the parties choice, disputes shall be subject to binding arbitration on conditions that are mutually agreed by the parties. (*Consensus*)

Article 6. Liability and Indemnity

To be agreed by the parties.

Article 8. Privileges and Immunity

Nothing in or relating to these clauses shall imply the obligation of WHO to submit to any national legislation or jurisdiction, or be deemed a waiver of any of the privileges and immunities of WHO in conformity with the Convention on the Privileges and Immunities of the Specialized Agencies approved by the General Assembly of the United Nations on November 21, 1947 or otherwise under any national or international law, convention or agreement.

Article 9. Name and Emblem

To be agreed by the parties.

Article 10. Warranties

To be agreed by the parties

Article 11. Duration of Agreement

To be agreed by the parties.

Article 12. Termination

To be agreed by the parties.

Article 13. Force Majeure

To be agreed by the parties.

Article 14. Governing law

To be agreed by the parties.

Article 15. Signature and Acceptance

In WITNESS Whereof, this Agreement has been duly executed by the parties.

SIGNED for and on behalf of WHO

SIGNED for and on behalf of Recipient

Signature _____

Signature _____

Name _____

Name _____

Title _____

Title _____

Annex

To be agreed by the parties.

ANNEX 3

ADVISORY GROUP TERMS OF REFERENCE (*CONSENSUS*)

(Adopted by the Intergovernmental Meeting at its resumed session in December 2008, as amended.)

1. Background and mandate of Advisory Group

The Interim Statement adopted by WHO Member States attending the session of the Intergovernmental Meeting on Pandemic Influenza Preparedness on 20–23 November 2007 urged action to develop fair, transparent, and equitable international mechanisms on virus sharing and benefit sharing. Member States called on the Director-General to establish an Advisory Mechanism to monitor, provide guidance to strengthen the functioning of the trust-based system needed to protect public health and undertake necessary assessment of that system. To carry this out, Member States specified that an Advisory Group will be appointed by the Director-General in consultation with Member States, based on equitable representation of the WHO regions and of affected countries.

The trust-based system is now referred to as the “Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits” (hereinafter “the Framework”). The scope of the Advisory Group is to monitor, assess and report on the system for sharing H5N1 influenza viruses and other influenza viruses with human pandemic potential as well as access to vaccines and other benefits of the Framework. The institutional components of the Framework to be monitored by the Advisory Group are National Influenza Centres, Other authorized laboratories, WHO Collaborating Centres, H5 Reference Laboratories, and Essential Regulatory Laboratories, as defined in Section 4 of the Framework. The pharmaceutical industry, although not included, can be consulted by the Advisory Group.

2. Functions of the Advisory Group

2.1 To monitor, assess and report on how the different functions of the Framework are implemented by its components. The information to conduct these tasks should be provided by the WHO Secretariat and other independent sources, if available. Monitoring by the Advisory Group will enable ongoing assessment of the functioning of the Framework and should include at least:

- (a) the rapid, systematic and timely sharing of H5N1 and other influenza viruses with human pandemic potential with the WHO GISRS;
- (b) the Influenza Virus Traceability Mechanism;
- (c) the global improvement of laboratory capacity, particularly in developing countries, to enhance pandemic influenza preparedness;
- (d) the fair and equitable sharing of benefits.
- (e) the use of financial and non-financial contributions.

2.2 To carry out the necessary assessment of the Framework according to quantitative and qualitative indicators developed from information provided by the WHO Secretariat and other independent sources, if necessary.

2.3 To provide guidance to strengthen the functioning of the Framework to the Director-General.

2.4 To make recommendations to the Director-General on the use of financial and non-financial contributions.

2.5 Recommendations and reports of the Advisory Group shall be evidence based.

2.6 To report annually, through the Director-General to the Executive Board and the World Health Assembly on its activities.

3. Nomination of members

3.1 The Advisory Group will comprise 18 members drawn from three Member States in each WHO region, with a skill mix of internationally recognized policy makers, public health experts and technical experts in the field of influenza. In the exercise of their functions the Members shall act as international experts serving WHO exclusively.

3.2 Each member will serve for three years. The duration of appointment of each member will be three years with a renewal of one third of the members every year; replacements must maintain the equitable representation of the six WHO regions and affected countries; all members will be eligible for two appointments. In the event of resignation or incapacity of a member for any reason, the Director-General will appoint a replacement member with a view to maintaining the equitable representation of the six WHO regions and affected countries. The replacement will complete the term of the previous member. The Group will select from among its members, a Chairperson and a Vice-Chairperson. The Chairperson and Vice-Chairperson will serve for two years after which another Chairperson and Vice-Chairperson will be selected by the Group members.

3.3 The Director-General will regularly accept nominations of representatives and will draw from this list to replace outgoing members with a view to maintaining the equitable representation of the six WHO regions and affected countries.

4. Working procedures

4.1 The Director-General will apply to this Advisory Group working procedures consistent with WHO's practices and procedures.

4.2 The Regulations for Expert Advisory Panels and Committees will apply to the Advisory Group, including with respect to the private nature of meetings. Furthermore, members of the Advisory Group will not make public statements, individually or on behalf of the Group, on the work of the Advisory Group, except as authorized in connection with reporting requirements or by the Director-General.

5. Resources for implementation

The Director-General will make available the necessary human and financial resources to support the work of the Advisory Group.

ANNEX 4

GUIDING PRINCIPLES FOR THE DEVELOPMENT OF TERMS OF REFERENCE FOR CURRENT AND POTENTIAL FUTURE WHO GISRS LABORATORIES FOR H5N1 AND OTHER HUMAN PANDEMIC INFLUENZA VIRUSES (*CONSENSUS*)

The specific roles, responsibilities and activities conducted by the different WHO GISRS laboratories can differ depending on whether they are a National Influenza Centre, a WHO Collaborating Centre, an H5 Reference Laboratory or an essential regulatory laboratory. However, in the context of pandemic influenza preparedness and their work with H5N1 and other viruses of human pandemic potential, the development of the Terms of Reference for each group of WHO GISRS laboratories shall comply with the following core guiding principles.

1. All activities conducted by WHO GISRS laboratories under their WHO Terms of Reference will be consistent with the Framework and the Standard Material Transfer Agreement.
2. The WHO GISRS laboratories will be coordinated by, and provide support to, WHO.
3. The WHO GISRS laboratories will provide a timely summary report of laboratory analyses and on request any other available information on tests conducted, test results and associated risk assessment and risk response as is specified in their Terms of Reference.
4. The WHO GISRS laboratories will share experience and provide capacity strengthening support to WHO Member States where necessary.
5. The WHO GISRS laboratories will provide support as specified in their Terms of Reference for the development of potential pandemic vaccine, pandemic vaccine, diagnostic test materials and pharmaceuticals.
6. If WHO GISRS laboratories conduct research on influenza viruses received for public health surveillance purposes, they will do so in a manner that includes participation of scientists, to the fullest extent possible, from the submitting National Influenza Centre or Other authorized laboratory, especially those from developing countries, including through the publication process.
7. The WHO GISRS laboratories will support global public health preparedness and response, especially for urgent situations including international outbreaks and epidemics.
8. The WHO GISRS laboratories will share in a rapid, systematic and timely manner PIP Biological Materials, using the Influenza Virus Traceability Mechanism as appropriate, including distribution to other qualified laboratories, to facilitate public health risk assessment, risk response activities and scientific research in accordance with the Standard Material Transfer Agreement.
9. The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.
10. The originating laboratories which provide the PIP Biological Materials received by the WHO GISRS laboratories will be given due credit and recognition.

ANNEX 5

WHO COLLABORATING CENTRES FOR INFLUENZA

TERMS OF REFERENCE RELATED TO WORK WITH PANDEMIC INFLUENZA PREPAREDNESS BIOLOGICAL MATERIALS (*Consensus*)

BACKGROUND

The WHO GISRS serves as a global alert mechanism for the emergence of influenza viruses with important features, including those with pandemic potential. For activities related to pandemic influenza, the WHO GISRS includes four complementary categories of institutions and laboratories: National Influenza Centres, WHO Collaborating Centres, WHO H5 Reference Laboratories and Essential Regulatory Laboratories. The WHO GISRS is coordinated by the WHO Global Influenza Programme. Within each category all institutions and laboratories perform functions defined by core Terms of Reference. The core Terms of Reference for WHO Collaborating Centres are the minimum requirements that must be met by each WHO Collaborating Centre and the capacity to fulfil these is a prerequisite to designation as a WHO Collaborating Centre. Each laboratory or institution that is formally recognized or designated as a part of WHO GISRS by WHO has accepted to be bound by the core Terms of Reference applicable to its category. The following are the core Terms of Reference applicable to the WHO Collaborating Centres.

In addition, individual WHO Collaborating Centres within the WHO GISRS may have additional Specific Terms of Reference, where appropriate. The Specific Terms of Reference recognize that there are differences in expertise, capacities and interests among the WHO Collaborating Centres and provide for individual WHO Collaborating Centres to perform additional functions related to pandemic risk assessment and response. Specific Terms of Reference will be discussed with and agreed upon between the WHO Collaborating Centre and the WHO Global Influenza Programme before the WHO Collaborating Centre's designation and redesignation.

In general, the WHO Collaborating Centres conduct influenza pandemic risk assessment on an ongoing basis and provide advice, expertise and support to Member States and the Secretariat to facilitate activities in response to influenza risks. The WHO Collaborating Centres support outbreak investigation, conduct comprehensive virus analyses, and select and develop candidate influenza vaccine viruses with pandemic potential. The efficient implementation pandemic influenza risk assessment and risk response is based on the collective efforts of all WHO GISRS members and through the rapid sharing of biological materials, reference reagents, epidemiologic data and other information.

It is understood that the Guiding Principles, as agreed by the Intergovernmental Meeting and reproduced below, will guide all activities, specific Terms of Reference or associated functions of the WHO GISRS laboratories when they act in their capacity as a WHO GISRS laboratory. The Terms of Reference for all WHO GISRS laboratories have been developed under the following overarching Guiding Principles:

Guiding Principles for the development of Terms of Reference for current and potential future WHO GISRS laboratories for H5N1 and other human pandemic influenza viruses

1. *All activities conducted by WHO GISRS laboratories under their WHO Terms of Reference will be consistent with the Framework and the Standard Material Transfer Agreement.*
2. *The WHO GISRS laboratories will be coordinated by, and provide support to, WHO.*
3. *The WHO GISRS laboratories will provide a timely summary report of laboratory analyses and on request any other available information on tests conducted, test results and associated risk assessment and risk response as is specified in their Terms of Reference.*
4. *The WHO GISRS laboratories will share experience and provide capacity strengthening support to WHO Member States within their resources where necessary.*
5. *The WHO GISRS laboratories will provide support as specified in their Terms of Reference for the development of potential pandemic vaccine, pandemic vaccine, diagnostic test materials and pharmaceuticals.*
6. *If WHO GISRS laboratories conduct research on influenza viruses received for public health surveillance purposes, they will do so in a manner that includes participation of scientists, to the fullest extent possible, from the submitting National Influenza Centre or other authorized laboratory, especially those from developing countries, including through the publication process.*
7. *The WHO GISRS laboratories will support global public health preparedness and response, especially for urgent situations including international outbreaks and epidemics.*
8. *The WHO GISRS laboratories will share in a rapid, systematic and timely manner biological materials related to pandemic influenza preparedness, using the Influenza Virus Traceability Mechanism as appropriate, including distribution to other qualified laboratories, to facilitate public health risk assessment, risk response activities and scientific research in accordance with the Standard Material Transfer Agreement.*
9. *The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.*
10. *The originating laboratories which provide the PIP Biological Materials received by the WHO GISRS laboratories will be given due credit and recognition.*

Core Terms of Reference

WHO Collaborating Centres for Influenza are centres of excellence on influenza which are designated by WHO and which agree to the following:

A. General conditions and activities

1. Work under the coordination of the WHO Global Influenza Programme, and provide support to WHO (Guiding Principles 2, 7);
2. fulfil the Core Terms of Reference and Specific Terms of Reference using financial support provided only by governmental and/or other non-commercial sources;
3. use the WHO Influenza Virus Traceability Mechanism to record the receipt and transfer of PIP Biological Materials (Guiding Principle 8);

4. comply with the Standard Material Transfer Agreement of the Pandemic Influenza Preparedness Framework for Sharing of Influenza viruses and access to vaccines and other benefits. (Guiding Principle 1);
5. maintain the capacity to exchange materials and information on a regular and timely basis with other WHO Collaborating Centres (Guiding Principles 3, 8);
6. have full and unrestricted access to biosafety level 3 laboratory facilities that meet recognized international and national standards. The Provider assumes full responsibility for complying with their respective national biosecurity and biosafety regulations on the understanding that such regulations and rules shall, at a minimum, meet the relevant and current WHO standards;
7. serve as a technical resource to WHO for any other urgent issues related to pandemic influenza or influenza outbreaks with pandemic potential (Guiding Principles 2, 5);
8. appropriately acknowledge the originating laboratories providing clinical specimens and/or influenza viruses with pandemic potential (Guiding Principles 8, 10);
9. maintain and strengthen active communication and collaboration with National Influenza Centres¹ and WHO to ensure that up-to-date information and findings of public health significance are rapidly exchanged (Guiding Principles 3, 4, 7, 8);
10. alert WHO and the country from which clinical specimens and/or viruses with pandemic potential were provided, on unusual findings related to pandemic influenza risk assessment (Guiding Principles 3, 7);
11. provide expertise and laboratory support when requested by WHO, to assist Member States, and in particular developing countries, in responding to outbreaks of influenza viruses with pandemic potential and risk assessment (Guiding Principles 2, 3, 4, 7);
12. provide training and laboratory support to National Influenza Centres, especially those in developing countries, on laboratory techniques and skills, including diagnosis, data analyses, risk assessment and other critical capacities (Guiding Principle 4);
13. assist WHO in improving global surveillance for influenza viruses with pandemic potential (Guiding Principles 2, 7) including the development of standards, recommendations and policies as well as improving associated outbreak response and pandemic preparedness (Guiding Principles 2, 3, 4, 7);
14. provide regular and timely surveillance data and results of virus characterization to originating laboratories and to WHO (Guiding Principle 3, 7);
15. advise the WHO GISRS on laboratory methods for diagnosis of influenza viruses with pandemic potential, including the adoption of new diagnostic approaches, the improvement of laboratory practices and other operational needs (Guiding Principles 2, 3, 5).

¹ WHO designated National Influenza Centres <http://www.who.int/csr/disease/influenza/centres/en/index.html>.

B. Laboratory analyses and related activities

1. Conduct accurate laboratory diagnosis, typing and subtyping, and confirmation of influenza A(H5) and other influenza viruses with pandemic potential for specimens received (Guiding Principles 2, 3, 7);
2. conduct isolation of influenza viruses with pandemic potential in embryonated eggs and cell culture;
3. conduct detailed antigenic and genetic analyses of influenza viruses with pandemic potential and make the results available to WHO and the originating laboratories in a timely manner (Guiding Principles 2, 3, 4, 7);
4. share available haemagglutinin, neuraminidase and other gene sequences of A(H5) and other influenza viruses with pandemic potential immediately with the originating laboratory, WHO Collaborating Centres and H5 Reference Laboratories (Guiding Principle 3);
5. upload available haemagglutinin, neuraminidase and other gene sequences of A(H5) and other influenza viruses with pandemic potential to a publicly accessible database in a timely manner but no later than three months after sequencing is completed, unless otherwise instructed by the laboratory or country providing the clinical specimens and/or viruses (Guiding Principle 9);
6. produce and distribute ferret antisera against influenza viruses with pandemic potential to WHO laboratories involved in influenza vaccine virus selection and development (Guiding Principle 5);
7. conduct analyses, provide data and advice to WHO and participate in meetings and teleconferences concerning the selection, development and timely availability of candidate vaccine viruses for H5N1 and other influenza viruses with pandemic potential (Guiding Principles 2, 5, 7);
8. participate in the development of candidate influenza vaccine viruses for pandemic influenza preparedness and response (Guiding Principles 5, 7);
9. conduct antiviral susceptibility testing of H5N1 and other influenza viruses with pandemic potential and provide timely reports to the originating laboratories and WHO (Guiding Principle 3);
10. select, maintain and update a group of reference influenza viruses with pandemic potential, including H5N1, and corresponding antisera if available and update the availability of candidate influenza vaccine viruses and corresponding antisera, if any, to WHO (Guiding Principles 2, 3, 5, 7);
11. develop, update and produce laboratory diagnostic reagents for influenza H5N1 and other viruses with pandemic potential directly or through contracted entities, and distribute them to National Influenza Centres subject to the availability of resources (Guiding Principle 5);
12. share in a timely manner clinical specimens and influenza viruses with pandemic potential in accordance with the Standard Material Transfer Agreement with laboratories working in coordination and collaboration with the WHO Global Influenza Programme, including:
 - (i) other WHO Collaborating Centres (Guiding Principles 1, 8);
 - (ii) essential regulatory laboratories that are involved in the WHO process of candidate influenza vaccine virus selection and development, as well as vaccine potency reagent development (Guiding Principles 1, 8);
 - (iii) other laboratories involved in WHO coordinated specialized activities (e.g. the WHO External Quality Assessment Project for the detection of subtype influenza A viruses using polymerase chain reaction; the WHO influenza polymerase chain reaction primer updating), and

other activities whose purpose is to strengthen global influenza surveillance and other risk assessment and risk response; as well as capacity building (Guiding Principles 1, 4, 8);

13. select candidate influenza vaccine viruses under the coordination of WHO, for development and production of vaccines against influenza viruses with pandemic potential. Depending on the vaccine production process, the candidate influenza vaccine viruses can include wild type viruses and high-growth reassortant viruses, including those prepared by reverse genetics. Distribute candidate influenza vaccine viruses to appropriate recipients with appropriate biosafety level capacity on request, including influenza vaccine manufacturers, diagnostic companies, research institutes and others interested in receiving influenza vaccine viruses (Guiding Principles 5, 8);

14. select, maintain and update reference A(H5N1) and other influenza viruses with pandemic potential as antigenically and genetically representative of important groups of viruses. Subject to the availability of resources, distribute both reference viruses and corresponding antisera, on request, to National Influenza Centres and other institutes for non-commercial activities including surveillance, and reference and research (Guiding Principle 10);

C. Research and scientific presentations and publications

1. Actively seek the participation of scientists from originating laboratories/countries in scientific projects associated with research on clinical specimens and/or influenza viruses from their countries and actively engage them in preparation of manuscripts for presentation and publication (Guiding Principle 6);

2. appropriately acknowledge in presentations and publications, the contributions of collaborators, including laboratories/countries providing clinical specimens or influenza viruses with pandemic potential or reagents, using guidelines such as those outlined by the International Committee of Medical Journal Editors¹ (Guiding Principle 6).

Specific Terms of Reference

These are additional functions attributed to an individual WHO Collaborating Centre in light of its specific expertise in the field of influenza. (*Consensus*)

¹ See <http://www.icmje.org/>.

NATIONAL INFLUENZA CENTRES

TERMS OF REFERENCE RELATED TO WORK WITH PANDEMIC INFLUENZA PREPAREDNESS BIOLOGICAL MATERIALS (*CONSENSUS*)

BACKGROUND

The WHO GISRS serves as a global alert mechanism for the emergence of influenza viruses with important features, including those with pandemic potential. For activities related to pandemic influenza, the WHO GISRS includes four complementary categories of institutions and laboratories: National Influenza Centres, WHO Collaborating Centres, WHO H5 Reference Laboratories and Essential Regulatory Laboratories. The WHO GISRS is coordinated by the WHO Global Influenza Programme. Within each category all institutions and laboratories perform functions defined by core Terms of Reference. Each laboratory or institution that is formally recognized or designated as a part of the WHO GISRS by WHO has accepted to be bound by the core Terms of Reference applicable to its category. The following are the core Terms of Reference applicable to the National Influenza Centres.

National Influenza Centres play a key role in pandemic influenza risk assessment by alerting WHO immediately to outbreaks of H5N1 or other influenza viruses with pandemic potential. National Influenza Centres collect specimens from suspected cases of H5N1 or other unusual influenza viral infection, perform laboratory diagnosis and analysis, and ship in a timely manner, such specimens or viruses isolated from them, to a WHO Collaborating Centre or H5 Reference Laboratory for advanced virological analysis. Efficient pandemic influenza risk assessment and risk response are based on collective efforts from all WHO GISRS members through rapid exchange of biological materials, reference reagents, epidemiologic data and other information.

It is understood that the Guiding Principles, as agreed by the Intergovernmental Meeting and reproduced below, will guide all activities, specific Terms of Reference or associated functions of the WHO GISRS laboratories when they act in their capacity as a WHO GISRS laboratory. The Terms of Reference for all WHO GISRS laboratories have been developed under the following overarching Guiding Principles:

Guiding Principles for the development of Terms of Reference for current and potential future WHO GISRS laboratories for H5N1 and other human pandemic influenza viruses

- 1. All activities conducted by WHO GISRS laboratories under their WHO Terms of Reference will be consistent with the Framework and the Standard Material Transfer Agreement.*
- 2. The WHO GISRS laboratories will be coordinated by, and provide support to, WHO.*
- 3. The WHO GISRS laboratories will provide a timely summary report of laboratory analyses and on request any other available information on tests conducted, test results and associated risk assessment and risk response as is specified in their Terms of Reference.*
- 4. The WHO GISRS laboratories will share experience and provide capacity strengthening support to WHO Member States within their resources where necessary.*
- 5. The WHO GISRS laboratories will provide support as specified in their Terms of Reference for the development of potential pandemic vaccine, pandemic vaccine, diagnostic test materials and pharmaceuticals.*
- 6. If WHO GISRS laboratories conduct research on influenza viruses received for public health surveillance purposes, they will do so in a manner that includes participation of scientists, to the*

fullest extent possible, from the submitting National Influenza Centre or other authorized laboratory, especially those from developing countries, including through the publication process.

7. *The WHO GISRS laboratories will support global public health preparedness and response, especially for urgent situations including international outbreaks and epidemics.*
8. *The WHO GISRS laboratories will share in a rapid, systematic and timely manner PIP Biological Materials, using the Influenza Virus Traceability Mechanism as appropriate, including distribution to other qualified laboratories, to facilitate public health risk assessment, risk response activities and scientific research in accordance with the Standard Material Transfer Agreement.*
9. *The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.*
10. *The originating laboratories which provide the PIP Biological Materials received by the WHO GISRS laboratories will be given due credit and recognition.*

Core Terms of Reference

National Influenza Centres are laboratories that fulfil the Terms of Reference listed below. A National Influenza Centre is formally designated by the health ministry of the country concerned and is recognized by WHO. A National Influenza Centre may have additional obligations under the authority of its Ministry of Health.

A. General conditions and activities

1. Work under the coordination of the WHO Global Influenza Programme and provide support to WHO (Guiding Principles 2, 7);
2. use the WHO Influenza Virus Traceability Mechanism to record the receipt and transfer of PIP Biological Materials (Guiding Principle 8);
3. comply with the Standard Material Transfer Agreement of the Pandemic Influenza Preparedness Framework for Sharing of Influenza viruses and access to vaccines and other benefits (Guiding Principle 1);
4. serve as a key point of contact between WHO and the country of the National Influenza Centre on issues related to surveillance, laboratory diagnosis, and sharing of clinical specimens and/or influenza viruses with pandemic potential, as well as sharing of important related clinical or epidemiological information, when available, with WHO (Guiding Principles 2, 3, 4, 7, 8);
5. participate actively in WHO pandemic influenza surveillance activities and maintain active communication and collaboration with other members of the WHO GISRS (Guiding Principles 4, 7, 8).

B. Laboratory and related activities

1. Collect or process as appropriate clinical specimens from patients suspected to be infected with H5N1 and other influenza viruses with pandemic potential (Guiding Principle 7);

2. act as a collection point for virus isolates of suspected pandemic influenza from laboratories within the country;
3. conduct testing of clinical specimens for influenza viruses and detect influenza viruses that cannot be readily identified with diagnostic reagents provided through the WHO GISRS;
4. ship, within one week, clinical specimens and/or viruses that cannot be readily identified with diagnostic reagents provided through the WHO GISRS to a WHO Collaborating Centre or H5 Reference Laboratory of their choice of and include the date the specimen was collected and relevant geographical, epidemiological and clinical information (Guiding Principles 2, 3, 5, 7, 8); (*Consensus*)
5. attend laboratory training courses provided by the WHO Collaborating Centres in an effort to establish and maintain capacity to recognize influenza viruses that cannot be readily identified (Guiding Principle 4);
6. review, maintain and strengthen influenza surveillance in the country (Guiding Principle 2);
7. provide technical advice and support to other influenza laboratories in the country on specimen collection and shipment logistics, laboratory biosafety and other operational procedures related to influenza surveillance (Guiding Principles 2, 7).

C. Information and communication

1. Alert WHO immediately when influenza viruses are detected that cannot be readily identified with diagnostic reagents provided through the WHO GISRS or when unusual outbreaks of non-seasonal influenza or influenza-like illness emerge;
2. provide national authorities and the general public with information on H5N1 and other influenza viruses with pandemic potential circulating in the country in a timely manner.

D. Research, Scientific Presentations and Publications

1. Actively seek the participation of scientists from originating laboratories/countries in scientific projects associated with research on clinical specimens and/or influenza viruses from their countries and actively engage them in preparation of manuscripts for presentation and publication (Guiding Principle 6);
2. appropriately acknowledge in presentations and publications, the contributions of collaborators, including laboratories/countries providing clinical specimens or influenza viruses with pandemic potential or reagents, using guidelines such as those outlined by the International Committee of Medical Journal Editors¹ (Guiding Principle 6).

¹ See <http://www.icmje.org/>.

WHO H5 REFERENCE LABORATORIES

TERMS OF REFERENCE RELATED TO WORK WITH PANDEMIC INFLUENZA PREPAREDNESS BIOLOGICAL MATERIALS (*CONSENSUS*)

BACKGROUND

The WHO GISRS serves as a global alert mechanism for the emergence of influenza viruses with important features, including those with pandemic potential. For activities related to pandemic influenza, the WHO GISRS includes four complementary categories of institutions and laboratories: National Influenza Centres, WHO Collaborating Centres, WHO H5 Reference Laboratories and Essential Regulatory Laboratories. The WHO GISRS is coordinated by the WHO Global Influenza Programme. Within each category all institutions and laboratories perform functions defined by core Terms of Reference. The core Terms of Reference for WHO Collaborating Centres are the minimum requirements that must be met by each WHO Collaborating Centre and the capacity to fulfil these is a prerequisite to designation as a WHO Collaborating Centre. Each laboratory or institution that is formally recognized or designated as a part of the WHO GISRS by WHO has accepted to be bound by the core Terms of Reference applicable to its category. The following are the core Terms of Reference applicable to the H5 Reference Laboratories.

WHO H5 Reference Laboratories are laboratories that were designated by WHO on an *ad hoc basis* commencing in 2005, to support the WHO GISRS in response to the emergence and spread of highly pathogenic avian influenza H5N1. These laboratories conduct influenza risk assessment and response by providing reliable laboratory diagnosis of influenza infection in humans, especially those suspected of being associated with avian influenza A(H5) viruses or other influenza viruses with pandemic potential. Efficient influenza risk assessment and risk response are based on collective efforts from all WHO GISRS members through rapid exchange of biological materials, reference reagents, epidemiologic data and other information.

It is understood that the Guiding Principles, as agreed by the Intergovernmental Meeting and reproduced below, will guide all activities, specific Terms of Reference or associated functions of the WHO GISRS laboratories when they act in their capacity as a WHO GISRS laboratory. The Terms of Reference for all WHO GISRS laboratories have been developed under the following overarching Guiding Principles:

Guiding Principles for the development of Terms of Reference for current and potential future WHO GISRS laboratories for H5N1 and other human pandemic influenza viruses

1. *All activities conducted by WHO GISRS laboratories under their WHO Terms of Reference will be consistent with the Framework and the Standard Material Transfer Agreement.*
2. *The WHO GISRS laboratories will be coordinated by, and provide support to, WHO.*
3. *The WHO GISRS laboratories will provide a timely summary report of laboratory analyses and on request any other available information on tests conducted, test results and associated risk assessment and risk response as is specified in their Terms of Reference.*

4. *The WHO GISRS laboratories will share experience and provide capacity strengthening support to WHO Member States within their resources where necessary.*
5. *The WHO GISRS laboratories will provide support as specified in their Terms of Reference for the development of potential pandemic vaccine, pandemic vaccine, diagnostic test materials and pharmaceuticals.*
6. *If WHO GISRS laboratories conduct research on influenza viruses received for public health surveillance purposes, they will do so in a manner that includes participation of scientists, to the fullest extent possible, from the submitting National Influenza Centre or other authorized laboratory, especially those from developing countries, including through the publication process.*
7. *The WHO GISRS laboratories will support global public health preparedness and response, especially for urgent situations including international outbreaks and epidemics.*
8. *The WHO GISRS laboratories will share in a rapid, systematic and timely manner PIP Biological Materials, using the Influenza Virus Traceability Mechanism as appropriate, including distribution to other qualified laboratories, to facilitate public health risk assessment, risk response activities and scientific research in accordance with the Standard Material Transfer Agreement.*
9. *The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.*
10. *The originating laboratories which provide the PIP Biological Materials received by the WHO GISRS laboratories will be given due credit and recognition.*

Core Terms of Reference

WHO H5 Reference Laboratories are laboratories which are designated through a defined WHO process, on an *ad hoc basis*, and which meet the core Terms of Reference listed below.

A. General conditions and activities

1. Work under the coordination of the WHO Global Influenza Programme; and provide support to WHO (Guiding Principle 2);
2. meet the WHO criteria for accepting positive results of H5 infection in humans;¹
3. use the WHO Influenza Virus Traceability Mechanism to record the receipt and transfer of PIP Biological Materials (Guiding Principle 8);
4. comply with the Standard Material Transfer Agreement of the PIP Framework for Sharing of Influenza viruses and access to vaccines and other benefits. (Guiding Principle 1);
5. provide laboratory services to its own country and other countries when needed for diagnosis of influenza A(H5) and other influenza viruses with pandemic potential (Guiding Principles 3, 7);
6. alert WHO and the country that provided clinical specimens and/or viruses with pandemic potential about unusual findings related to pandemic influenza risk assessment (Guiding Principles 3, 7);
7. provide feedback to WHO on the use of WHO recommended diagnostic protocols and primers to assist WHO in updating laboratory diagnostic recommendations (Guiding Principles 2, 3, 4, 5).

¹ See http://www.who.int/csr/disease/avian_influenza/H5AcceptanceCriteria_16Oct07.pdf.

B. Laboratory and other activities

1. Provide advice to clinics, hospitals and other specimen collection sites on safe and appropriate clinical specimen collection, storage, packaging and shipping (Guiding Principle 7);
2. conduct accurate laboratory diagnosis, typing and subtyping and confirmation of influenza A(H5) and other influenza viruses with pandemic potential for specimens received and make the results available to WHO Collaborating Centres and the originating laboratories in a timely manner (Guiding Principles 2, 3, 4, 7);
3. provide expertise and laboratory support in response to outbreaks of A(H5) and other influenza viruses with pandemic potential (Guiding Principles 2, 3, 4, 5, 7);
4. routinely share clinical specimens and/or virus isolates from A(H5) and other influenza viruses with pandemic potential with WHO Collaborating Centres for further characterization in accordance with [the Standard Material Transfer Agreement] (Guiding Principles 1, 8, 10);
5. share available haemagglutinin, neuraminidase and other gene sequences of A(H5) and other influenza viruses with pandemic potential immediately with the originating laboratory, WHO Collaborating Centres and H5 Reference Laboratories (Guiding Principle 3);
6. upload available haemagglutinin, neuraminidase and other gene sequences of A(H5) and other influenza viruses with pandemic potential to a publicly accessible database in a timely manner, but no later than three months after sequencing is completed, unless otherwise instructed by the laboratory or country providing the clinical specimens and/or viruses (Guiding Principle 9);
7. appropriately acknowledge the originating laboratories providing clinical specimens and/or influenza viruses with pandemic potential (Guiding Principles 8, 10).

C. Research, scientific presentations and publications

1. Actively seek the participation of scientists from originating laboratories/countries in scientific projects associated with research on clinical specimens and/or influenza viruses from their countries and actively engage them in preparation of manuscripts for presentation and publication (Guiding Principle 6);
2. appropriately acknowledge in presentations and publications, the contributions of collaborators, including laboratories/countries providing clinical specimens or influenza viruses with pandemic potential or reagents, using guidelines such as those outlined by the International Committee of Medical Journal Editors¹ (Guiding Principle 6).

¹ See <http://www.icmje.org/>.

ESSENTIAL REGULATORY LABORATORIES

TERMS OF REFERENCE RELATED TO WORK WITH PANDEMIC INFLUENZA PREPAREDNESS BIOLOGICAL MATERIALS (*CONSENSUS*)

BACKGROUND

The WHO GISRS serves as a global alert mechanism for the emergence of influenza viruses with important features, including those with pandemic potential. For activities related to pandemic influenza, the WHO GISRS includes four complementary categories of institutions and laboratories: National Influenza Centres, WHO Collaborating Centres, WHO H5 Reference Laboratories and Essential Regulatory Laboratories. The WHO GISRS is coordinated by the WHO Global Influenza Programme. Within each category all institutions and laboratories perform functions defined by core Terms of Reference. The core Terms of Reference for WHO Collaborating Centres are the minimum requirements that must be met by each Collaborating Centre and the capacity to fulfil these is a prerequisite to designation as a WHO Collaborating Centre. Each laboratory or institution that is formally recognized or designated as a part of the WHO GISRS by WHO has accepted to be bound by the core Terms of Reference applicable to its category. The following are the core Terms of Reference applicable to the Essential Regulatory Laboratories.

Essential Regulatory Laboratories are formally associated with national regulatory agencies, and have a critical role in developing, regulating and standardizing influenza vaccines. They have performed this role for nearly four decades within the WHO GISRS, and have thereby contributed to the production of safe and effective influenza vaccines through the selection and development of candidate vaccine viruses. While they previously had no formal Terms of Reference with WHO, in practice, they worked closely with both WHO and the influenza vaccine manufacturers. Currently there are four Collaborating Centres: the Center for Biologics Evaluation and Research, United States of America; the National Institute for Biological Standards and Control, United Kingdom of Great Britain and Northern Ireland; the National Institute for Infectious Diseases, Japan, and the Therapeutic Goods Administration, Australia.

The core Terms of Reference are the minimum requirements that must be met by each Essential Regulatory Laboratory, either individually or as a group. Specific Terms of Reference may be discussed with and agreed upon by the Essential Regulatory Laboratory, the WHO Global Influenza Programme and, in some cases, industry before recognition.

It is understood that the Guiding Principles, as agreed by the Intergovernmental Meeting and reproduced below, will guide all activities, specific Terms of Reference or associated functions of the WHO GISRS laboratories when they act in their capacity as a WHO GISRS laboratory. The Terms of Reference for all WHO GISRS laboratories have been developed under the following overarching Guiding Principles:

Guiding Principles for the development of Terms of Reference for current and potential future WHO GISRS laboratories for H5N1 and other human pandemic influenza viruses

- 1. All activities conducted by WHO GISRS laboratories under their WHO Terms of Reference will be consistent with the Framework and the Standard Material Transfer Agreement.*
- 2. The WHO GISRS laboratories will be coordinated by, and provide support to, WHO.*
- 3. The WHO GISRS laboratories will provide a timely summary report of laboratory analyses and on request any other available information on tests conducted, test results and associated risk assessment and risk response as is specified in their Terms of Reference.*

4. *The WHO GISRS laboratories will share experience and provide capacity strengthening support to WHO Member States within their resources where necessary.*
5. *The WHO GISRS laboratories will provide support as specified in their Terms of Reference for the development of potential pandemic vaccine, pandemic vaccine, diagnostic test materials and pharmaceuticals.*
6. *If WHO GISRS laboratories conduct research on influenza viruses received for public health surveillance purposes, they will do so in a manner that includes participation of scientists, to the fullest extent possible, from the submitting National Influenza Centre or other authorized laboratory, especially those from developing countries, including through the publication process.*
7. *The WHO GISRS laboratories will support global public health preparedness and response, especially for urgent situations including international outbreaks and epidemics.*
8. *The WHO GISRS laboratories will share in a rapid, systematic and timely manner PIP Biological Materials, using the Influenza Virus Traceability Mechanism as appropriate, including distribution to other qualified laboratories, to facilitate public health risk assessment, risk response activities and scientific research in accordance with the Standard Material Transfer Agreement.*
9. *The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.*
10. *The originating laboratories which provide the PIP Biological Materials received by the WHO GISRS laboratories will be given due credit and recognition.*

Core Terms of Reference

Essential Regulatory Laboratories meet the following core Terms of Reference listed below, either individually or as a group:

A. General conditions and activities

1. Advise WHO on the selection of H5N1 and other influenza viruses with pandemic potential for use in influenza vaccines (Guiding Principles 2, 3, 5);
2. assist WHO and Member States in developing vaccine-related aspects of preparedness and response plans for pandemic influenza (Guiding Principles 2, 3, 4, 7);
3. advise WHO on relevant regulatory and development aspects of vaccines for H5N1 and other influenza viruses with pandemic potential (Guiding Principles 2, 3, 5);
4. when requested, inform and advise WHO on work programmes and new technologies aimed at improving development and standardization of vaccines for H5N1 and other influenza viruses with pandemic potential (Guiding Principles 2, 3, 4, 5);
5. use the WHO Influenza Virus Traceability Mechanism to record the receipt and transfer of PIP Biological Materials (Guiding Principles 8);

6. comply with the Standard Material Transfer Agreement of the Pandemic Influenza Preparedness Framework for sharing of influenza viruses and access to vaccines and other benefits (Guiding Principle 1).

B. Laboratory and related activities

1. Store, and, if required, amplify representative H5N1 and other influenza viruses with pandemic potential obtained from the WHO GISRS for the purpose of developing influenza vaccine viruses (Guiding Principles 1, 2);

2. on request by WHO, develop candidate H5N1 and other influenza vaccine viruses with pandemic potential and characterize them using agreed standards (Guiding Principles 1, 2, 3, 5, 6);

3. store, and, if required, amplify candidate H5N1 and other influenza vaccine viruses with pandemic potential obtained from the WHO GISRS (Guiding Principles 1, 2, 3, 5);

4. prepare and calibrate reference reagents for standardization of candidate influenza vaccine viruses for H5N1 and other influenza viruses with pandemic potential in conjunction with other Essential Regulatory Laboratories (Guiding Principles 1, 2, 5);

5. distribute, subject to the Standard Material Transfer Agreement, candidate influenza vaccine viruses for H5N1 and other influenza viruses with pandemic potential to interested laboratories, including laboratories within the WHO GISRS and influenza vaccine manufacturers (Guiding Principles 1, 2, 5);

6. directly or through contractors, supply reference reagents for standardization of H5N1 and other potential pandemic influenza vaccines to laboratories, such as laboratories within the WHO GISRS, national regulatory laboratories and influenza vaccine manufacturers (Guiding Principles 1, 2, 5);

7. analyse, provide data and advice to WHO and participate in meetings and teleconferences concerning the selection, development and timely availability of candidate vaccine viruses for H5N1 and other influenza viruses with pandemic potential (Guiding Principles 2, 5, 7).

C. Research and scientific presentations and publications

1. Actively seek the participation of scientists from originating laboratories/countries in scientific projects associated with research on clinical specimens and/or influenza viruses from their countries and actively engage them in preparation of manuscripts for presentation and publication (Guiding Principle 6);

2. appropriately acknowledge in presentations and publications, the contributions of collaborators, including laboratories/countries providing clinical specimens or influenza viruses with pandemic potential or reagents, using guidelines such as those outlined by the International Committee of Medical Journal Editors¹ (Guiding Principle 6).

= = =

¹ See <http://www.icmje.org/>.