Note from the Secretariat:
In light of the particular importance and complexity of the issue of tracing and monitoring genetic sequence data, the PIP Advisory Group, as noted in A67/36 Add. 1, at paragraph 6¹, has planned to meet with electronic database managers for genetic sequence data as well as industry and other stakeholders during its meeting in October 2014, to gather further information with a view to developing advice to the Director-General on genetic sequence data-related issues.

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PART 1. BACKGROUND

In May 2011, the Sixty-fourth World Health Assembly adopted the Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits (or ‘PIP Framework’). This is an international arrangement that brings together Member States, industry, other key stakeholders, and WHO to implement a global approach to strengthen preparedness for the next influenza pandemic. The Framework took over four years to negotiate and reflects a common desire of countries to develop a more structured, efficient and equitable system for, *inter alia*, access to pandemic vaccines. It has a limited scope, covering only influenza viruses with human pandemic potential, but provides roles for countries, WHO, industry and other stakeholders.

**PIP Framework objectives**

The PIP Framework includes two objectives:

1) Ensure that countries share ‘influenza viruses with human pandemic potential’ or ‘IVPPs’ with a WHO-coordinated network of laboratories called “GISRS”. GISRS is an international network of public health laboratories that work on influenza. There are currently 141 laboratories in the network, in 111 countries. All the laboratories in the network operate under specific GISRS terms of reference. The guiding principles for those terms of reference include an obligation to “submit genetic sequences data [from H5N1 and other influenza viruses with human pandemic potential] to GISAID and GenBank or similar databases in a timely manner […].’’

- Under the PIP Framework, IVPPs are part of a broader set of materials called ‘PIP Biological Materials’ or ‘PIBM’ which include human clinical specimens, influenza virus isolates, extracted RNA, cDNA, and influenza candidate vaccine viruses developed from IVPPs by GISRS laboratories.

2) Share the benefits derived from the sharing of those IVPPs with all countries in need.

- Benefits may include, among others, pandemic influenza vaccines.
- Access to benefits such as vaccines is secured by WHO through agreements – known as ‘Standard Material Transfer Agreements 2’ or ‘SMTA2’ – concluded with, *inter alia*, manufacturers that receive candidate vaccine viruses from GISRS.
- Influenza vaccine, diagnostic and pharmaceutical manufacturers who use the WHO Global Influenza Surveillance and Response System (GISRS) pay an annual partnership contribution to WHO, which is used for activities that strengthen global readiness for, and response to, pandemic influenza.

**GSD and biosynthetic technologies**

Several laboratories are now able to synthesize influenza candidate vaccine viruses, and influenza virus proteins or antibodies *using only GSD*. Thus, for example:

- Novartis very recently announced positive phase I clinical trial results for a synthetic H7N9 vaccine using a sequence shared by the Chinese Center for Disease Control, which is a WHO Collaborating Centre for Reference and Research on Influenza.
Novavax reported positive phase I clinical trial results for an H7N9 vaccine using synthetic virus-like particle.\textsuperscript{10} BiondVax Pharmaceuticals designed a universal influenza vaccine using “a recombinant, fully synthetic protein made of several conserved regions of the flu virus”\textsuperscript{11}. The company recently completed phase II clinical trials with positive results.

These developments raised questions about the broader implications of use of IVPP GSD, which had been anticipated but not resolved by Member States when they adopted the PIP Framework. Indeed, Member States were aware that issues related to the use of IVPP GSD would arise due to the rapid development and application of biosynthetic technologies to the field of influenza research and vaccine production. Thus, they requested that “the Director-General consult with the Advisory Group on the best process for further discussion and resolution of issues relating to the handling of genetic sequence data”\textsuperscript{12}.

The PIP Framework Advisory Group (PIP AG) will therefore develop advice for the Director-General on this issue. To assist with this task, the PIP AG asked the Secretariat to convene a Technical Expert Working Group (TEWG) to provide the following:

1. An assessment of the \textit{scientific, technical, operational and intellectual property implications of using IVPP GSD} rather than physical materials for influenza research and vaccine production, including how the transfer of such data could be monitored.

2. An assessment of whether \textit{other significant implications} exist when using IVPP GSD for the purposes mentioned above or for the research and development of non-influenza products.

This report was drafted by the Technical Expert Working Group (TEWG) on genetic sequence data; Part 2 contains a discussion on the TEWG’s assessment of the many implications of using IVPP GSD. A list of abbreviations and acronyms, a glossary of terms, the methodology for the development of the report, and the list of TEWG experts may be found in Annexes 1, 2, 3 and 4 respectively.

\textbf{PART 2. DISCUSSION}

\textbf{1. Context}

\textit{1.1. Genetic Sequence Data and the PIP Framework}

The TEWG noted that there are different perspectives on whether genetic sequence data (GSD) are included in the definition of PIP biological material. While at present GSD is not expressly mentioned in the definition of PIP biological materials, the TEWG agreed that GSD falls within the PIP Framework (e.g. section 5.2; Annex 4, point 9; Annex 5 ‘Guiding Principles’), and that the spirit of the Framework and the importance of maintaining equal footing for the sharing of viruses and benefits derived therefrom, must be kept in mind in considering issues related to the handling of GSD for H5N1 and other influenza viruses with pandemic potential.

\textsuperscript{9} GISRS has 4 categories of laboratories: National Influenza Centers, Collaborating Centres, Essential Regulatory Laboratories, and H5 Reference Laboratories. Currently there are 6 Collaborating Centres located in Melbourne, Australia; Beijing, China; Tokyo Japan; London, UK; Atlanta, Georgia, USA; and Memphis, Tennessee, USA.


\textsuperscript{12} See Framework section 5.2.4.
The TEWG further noted that, on the one hand, preserving the integrity of the PIP Framework and the balance it achieved with regard to the sharing of viruses and the benefits arising therefrom will require the consideration of mechanisms to ensure the monitoring and/or tracing of the use of GSD or other mechanisms related to influenza-related products. In the absence of such mechanisms, and given the options open by the use of GSD for the development of vaccines, the attainment of essential objectives of the PIP Framework\textsuperscript{13} may be systematically frustrated. On the other hand however, it is essential that such mechanisms do not slow down the sharing of genetic sequence data.

2. Scientific, technical, operational and IP implications

2.1. What are the current known uses of GSD in relationship to influenza related technologies, products, inventions and patents?

Main direct uses of GSD

Direct refer to the use of a particular sequence to develop a product. A prime example is the production of ‘synthetic’ candidate vaccine viruses (CVVs) for vaccine development. In such case, a particular genetic sequence can be used directly to design synthetic DNA, which is then used to generate ‘synthetic’ CVVs.\textsuperscript{14}

Synthetic CVVs are in many ways not different from currently used CVVs, in particular those generated by reverse genetics (RG) technology. While the starting material is different between synthetic CVVs and currently used CVVs generated by RG technology, most steps in the generation of these CVVs are identical or very similar. For more traditional RG CVVs, nucleic acid (RNA) is extracted from viruses and converted into DNA; the DNA copies of genomic segments of influenza virus are then assembled into plasmid vectors that allow the expression of virus-like RNA molecules in cells, though the latter stage can take various forms and plasmids are not always used.\textsuperscript{15} Importantly, the genetic information is then introduced into a susceptible host cell, usually a cell line, where an infectious cycle is initiated de novo, leading to the production of influenza viruses containing the viral genetic information introduced into the cells.

The use of synthetic DNA allows this process to be carried out in the absence of any live influenza virus as a source of genetic information in the laboratory carrying out the process. Instead, GSD, obtained from the original virus\textsuperscript{16}, usually by another laboratory and shared via databases or bilaterally, is used to generate the nucleic acid (DNA) required for the construction of appropriate RG vectors. From this step onwards, normal RG procedures are followed, resulting in new RG viruses.

An example of the use of synthetic CVVs has been the experience with the H7N9 pandemic influenza strain in 2013. When the sequence for the H7N9 hemagglutinin (HA) and neuraminidase (NA) genes was posted on GISAID, this information was used immediately for the synthesis of the genes.\textsuperscript{17} The HA and NA synthetic genes were then used to transfect MDCK cells using plasmids coding for the

\textsuperscript{13} Principle 8 of the PIP Framework, in particular, recognizes ‘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’.
\textsuperscript{15} Engelhardt O, “Many ways to make an influenza virus – a review of influenza virus reverse genetics methods” (2013) \textit{Influenza Other Respir Viruses}, 7: 249.
\textsuperscript{16} This can potentially be done without actual virus isolation, by sequencing clinical specimens directly.
\textsuperscript{17} An in-vitro correction system allowing no more than 1 sequence error in 10,000 bases was used to generate the synthetic genes.
PR8 backbone. A CVV was prepared from MDCK cells, which was subsequently used for the production of a cell-based vaccine.\textsuperscript{18}

Alternatively, CVVs may be made from plasmids generated using GSD. In this process, instead of constructing a new RG vector using synthetic DNA, an existing plasmid construct containing a sequence with high similarity to the influenza sequence of interest is modified by site-directed mutagenesis to encode a protein corresponding to the sequence retrieved from a database. It is worth noting that the original plasmid construct itself may have been made using nucleic acid extracted from a virus as starting material.

The ability to use genetic sequence information has resulted, at least in part, in the emergence of new approaches to vaccine development and changes in the virus/vaccine pipeline in recent years. Speed is of the essence in the development of a vaccine for use as a counter-measure to a virus with human pandemic potential. An increasing number of vaccine manufacturers are using GSD as an alternative to conventional whole virus approaches making it possible to more rapidly develop vaccines. Technologies based on the recombinant expression of viral antigens generated using GSD will be critical over the next years and decades for both the development of completely new classes of vaccines and the modification of existing vaccine technologies. These include such approaches as recombinant hemagglutinin, e.g. Flublok (CDC 2013); virus-like particles (VLPs) (e.g., Novavax 2014); and fusion proteins (e.g., Vaxinnate, 2014).

An additional potential use of synthetic genes is the generation of nucleic acids vaccines. For example, Hekele \textit{et al.} developed a method to incorporate H7N9 synthetic genes into the Self Amplifying mRNA vaccines (SAM) platform. This completely synthetic vaccine was used to immunize mice only 8 days after the sequences were made available online through the GISAID database. Results from the study indicated that all immunized mice produced protective levels of antibodies in less than 40 days after the sequences were posted online.\textsuperscript{19} Also, novel vaccine development and manufacturing technologies are arising, which have demonstrated the effective use of GSD for rapid generation of vaccine candidates.\textsuperscript{20}

Related is the use of GSD for the identification of novel genomes or mixed infections. For example, the J. Craig Venter Institute’s viral finishing pipeline involves comparing the nucleic acid sequences of isolated or mixed influenza viruses against the gene sequences of all known influenza genes and potential open reading frames.\textsuperscript{21}

\textbf{Use of bulk sequences}

Bulk sequences consist of multiple gene or genome sequences that share a common denominator, such as a subtype, a mutation or a conserved region, and that are analysed or used in bulk. When bulk sequences are used, no single virus can be considered critical; as long as sufficient representative sequences are in public databases, the withholding of individual virus sequences by a laboratory or other holder of the virus (e.g., a country in which an outbreak has occurred) will not substantially affect these approaches. There is an important potential exception to this: new viruses (e.g. of a new

\textsuperscript{18} The same technology can also be used to make CVVs for egg-based vaccines.

\textsuperscript{19} Hekele A \textit{et al.}, “Rapidly produced SAM(reg) vaccine against H7N9 influenza is immunogenic in mice” (2013) \textit{Emerg Microbes Infect} 2: e52.

\textsuperscript{20} The biotech company Medicago, Inc. uses GSD to generate VLPs for its novel plant-based vaccine manufacture, developing candidate vaccines, for instance for H1N1 and H7N9 viruses, suitable for animal trials within three weeks from receipt of GSD.

subtype) for which few sequences are known or where the new viruses differ substantially from sequences already available.22

Bulk sequences may be used in basic research, applied research, public health and epidemiology. Researchers use this type of data to do evolutionary analysis of changes in viruses, including influenza viruses, and may use it to help predict the genomic structures of emerging disease microbes. For example, ‘genetic passports’ of seasonal and pandemic strains of influenza A and B have been created to document and classify all mutations that may influence virulence.23

Specific uses of bulk sequences include the identification of conserved epitopes for new types of vaccine, such as in efforts to develop universal influenza vaccines and other vaccines based on cell-mediated immunity.24 Additionally, bulk sequences may be used to design primers and probes for general basic research, quality control, or for the detection/diagnosis of novel viruses and in molecular surveillance of such outbreaks.25

Although validation of assays currently requires actual virus, or extracted nucleic acid, it is anticipated that these types of assays will move toward the use of synthetic DNA at some time in the foreseeable future.

**Indirect uses of GSD**

More indirectly, proteins generated from GSD may be used, for example, to derive antibodies for therapy, diagnostics, etc. Prediction of vaccine efficacy relies on data related to viral evolution obtained through genomic analysis of sequences from circulating viruses. Understanding global influenza migration and persistence is crucial for vaccine strain selection. Sequence data facilitate epidemiologic study for robust migration analysis of the virus.26 Finally, sequencing of high-yield influenza reassortants allows the identification of mutations related to improved growth properties.27 This has the potential to help in the design or selection of improved candidate vaccine viruses in the future.

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**Individual influenza virus genetic sequences can be used as a direct source for the development of products, such as candidate vaccine viruses or vaccines using recombinant proteins. Additionally, bulk sequences are used, inter alia, to gather epidemiological data, to design primers, probes and antibodies as well as for the design of vaccines based on conserved epitopes. Collectively, these approaches, all critical for the development of new and better vaccines, as well as significantly decreasing the time required to manufacture pandemic vaccines, depend crucially on the availability of GSD.**

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22 Including these sequences might affect results if there are differences in relevant regions.
25 For example, they were used for the recent identification of human infections with avian influenza A(H7N9) viruses in China.
2.2. *What are the prospects for any of these uses to result in commercial products?*

The use of recombinant DNA technology to generate candidate vaccine viruses from GSD for the production of influenza vaccines, as described in section 1.1, is already mature from a technical point of view, and is likely to become routine in the future. These CVVs can be rapidly generated and used to make both effective cell-based and egg-based vaccines. Furthermore, related technologies are now widely used for a variety of experimental vaccines where optimization for human codon usage markedly improves vaccine yield compared to native viral genes. This approach has been adopted routinely for a variety of DNA, viral vector, and VLP vaccine candidates, including HIV, filoviruses, and alphaviruses for example. Thus, there is increasing utilization of genetic information for the generation of clinically relevant vaccines and other therapeutic developments.

2.3. *What are the current issues (including regulatory pathways, IP issues, etc.) that must be resolved before commercialization or the licensing of products?*

**Access to GSD**

GSD can be accessed from various sources including electronic databases. Some of these databases could require, as a condition of access to the data, that the user contact the provider of the data if use of the data will lead to a product that can be commercialized.

**Regulatory Issues**

As discussed under question 1.1, CVVs generated using synthetic DNA are almost indistinguishable from currently used CVVs, in particular those generated by reverse (RG) genetics technology. While the starting material is different, most steps in the generation of these CVVs are identical or very similar. Currently, no vaccine generated using synthetic CVVs has received market authorization. There is however some experience in the regulatory system (such as the US Food and Drug Administration [FDA] or the European Medicines Agency [EMA]) with the use of RG viruses in inactivated and live attenuated influenza vaccines.

In both Europe (EMA) and the United States (FDA), no major obstacles for the approval of vaccines based on a CVV generated from synthetic DNA are foreseen. However, it is difficult to judge *a priori* the issues that may arise during the licensure of such products unless (i) specific regulatory guidance is issued by a national/regional regulatory agency or (ii) an applicant submits a market approval application to an authority, which will be assessed on its own merits. In the United States for example, the key statutory requirement for granting approval is the product’s safety and efficacy. Whether the product is derived from viral samples or GSD would not necessarily change this calculation – even though the information sought and review processes used by the regulatory authority may change depending on how the product is derived and developed.

Most likely, national regulatory authorities would take a similar approach to GSD developed vaccines as they have for approving vaccines made using CVVs prepared by RG technology. It is worth noting however that issues identified during an application to a national regulatory authority are only applicable to that particular regime; other national regulatory authorities may raise different questions.

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29 Such viruses are the most common type of CVVs for pre-pandemic and pandemic vaccines that have been developed or are being developed (e.g. against avian H5N1, H7N9, H7N3 and other viruses of pandemic potential).
30 Outside of the United States, Canada and Europe, there is limited experience with the approval of vaccines generated by reverse (RG) genetics technology.
Further, these regulatory authorities are not necessarily consistent between jurisdictions. The most well-known of this type of distinction is the difference between regulation at the level of the product (as done in the United States) and at the level of the process (as in the EU and several other countries). For most of these latter jurisdictions, it is assumed that viruses generated from synthetic DNA are or will be categorized in accordance with national or regional regulatory systems. Laboratories generating and working on such viruses thus do or will need to follow specific regulations, which may require obtaining certain permits or doing risk assessments.

Approval of Candidate Vaccine Viruses

In many jurisdictions, any particular CVV used by a manufacturer to produce a commercial/licensed vaccine has to be approved by the relevant regulatory authority. This approval can be done in different ways. It should be noted that detailed requirements for acceptability of CVVs may differ between countries. The example given illustrates the types of processes and requirements for CVVs that may be encountered, but does not in any way represent a global picture.

For instance, in Europe, the EMA issues a list of acceptable CVVs for use in influenza vaccines. No CVVs generated from synthetic DNA have been on this list as yet. However, there does not appear to be any reason why such CVVs could not be included on the list in the future. This would require that an applicant (e.g. an interested manufacturer) propose a CVV generated from synthetic DNA to the EMA. To be included, CVVs must be characterised and, in particular, certified to be antigenically similar. Currently, testing for antigenic appropriateness of a new CVV is done by WHO Collaborating Centres (CCs). In principle, CVVs generated from synthetic DNA could undergo the same testing at a WHO CC. However, if there are to be many more CVVs in the future that require testing, current resources at CCs may not suffice to conduct this testing in a timely manner, which could result in a bottleneck in the development of vaccines from CVVs generated from synthetic and semi-synthetic DNA.

Under EMA requirements, manufacturers must characterise their own seed material, generated from CVVs. For this analysis to be meaningful, it requires one or more viruses as comparator. Therefore, even when manufacturers are generating CVVs from synthetic DNA, the need for actual virus material may not be completely avoided. If the CVV in question represents a virus of pandemic potential, comparator viruses would most likely have to be obtained under the PIP Framework (under an SMTA2) if they originate from GISRS. Thus, manufacturers might be captured under the PIP Framework through their quality control testing. However, there are at least two scenarios that might lead to a manufacturer not being captured under the PIP Framework/SMTA2 in the strict sense: (1) If confirmation of antigenic appropriateness by a WHO CC is done on seed level material then this testing might suffice for both confirmation of antigenic appropriateness in general as well as for regulatory purposes, thus obviating the need to carry out extra antigenic characterisation by the manufacturer; (2) if antigenic analysis of seed material is subcontracted to another laboratory that has access to relevant comparator viruses, or has obtained them under the PIP Framework. However, a subcontractor should be considered an agent or acting on behalf of the manufacturer, or should otherwise conclude an SMTA2 in accordance with the PIP Framework.

Vaccines using recombinant proteins (e.g. VLPs, recombinant HA)

Novel platforms for influenza vaccines have been explored in recent years (see section 1.1), and at least one vaccine using recombinant HA antigen has received marketing authorisation in one

31 FDA requirements focus on the final product, not how such product is in principle constructed.
32 Testing involves the two-way hemagglutination inhibition test or ‘2-way HI test’, which requires testing all CVVs against raised ferret antiserum/antisera. Certified CVVs are usually announced on the WHO website.
33 This characterisation includes antigenic analysis (e.g. by HI assay).
country. While different regulations and guidelines will apply to certain aspects of recombinant products, the overall situation is not dissimilar to the one described above for more traditional influenza vaccines. The only substantial difference as compared to ‘conventional’ recombinant protein production is the starting material: synthetic DNA, generated using GSD, is used in the construction of plasmids or other vectors needed for the production of protein.

Pandemic approval of GSD-based vaccines

Regulatory agencies may respond to a pressing need, such as an emerging pandemic, in a variety of ways. This may include expedited review processes, but regulatory agencies can also be even more stringent in pandemic times by requiring more detailed data requirements for certain populations (e.g., children or the elderly), quality control preparation, marketing safety surveillance, or field assessment of vaccine efficacy. If a regulatory body categorizes vaccines made using synthetic CVVs as no different than a new seed strain, then these vaccines may simply fit into the existing regulatory frameworks, which may include requirement waivers in certain circumstances (such as emerging influenza strains of concern). Alternatively, if synthetic vaccines are categorized as a completely new process, it is possible that more stringent requirements would be imposed. Overall, if a country were to begin approving synthetic vaccines for seasonal influenza before an emergency, approval of a pandemic vaccine would likely be eased. Experience during the 2009 H1N1 pandemic however suggests that unexpected questions and delays could arise in pandemic situations and that use of novel products and approaches for the first time during a pandemic may create public and political concerns which have to be carefully managed.

The WHO’s prequalification of a vaccine developed from GSD is certainly influential, but would not necessarily be sufficient impetus for a regulatory authority to provide approval in a domestic jurisdiction. Beyond the variability, however, there may be good reason for Member States to consider harmonized regulatory pathways to speed vaccine development in a public health emergency of international concern.

National regulatory authorities would most likely take a similar approach to GSD developed vaccines as they have for approving vaccines made using CVVs prepared by RG technology. Although no additional obstacles for the approval of vaccines based on a CVV generated from synthetic DNA are foreseen, experience during the 2009 H1N1 pandemic suggests that unexpected questions and delays could arise in pandemic situations due to the use of novel products and approaches.

Intellectual Property Issues

35 It is also possible that a more relaxed or quicker regulatory approval process could be established.
36 Case Illustration: pH1N1: Following the emergence of the 2009 pandemic influenza virus strain pH1N1, vaccine manufacturers moved rapidly to adapt a variety of vaccine production processes to produce large amounts of the vaccine. Each country’s national regulatory authority responding to the pandemic imposed a particular regulatory process for approving pH1N1 vaccines, authorizing their importation, and overseeing their distribution. These processes ranged from one-time waivers of normal rules to detailed requirements for pediatric subgroup data, regulatory assessments capacity, quality control preparedness and capacity, and post marketing safety surveillance and field assessment of efficacy and immunogenicity. Some regulatory agencies, for example, approved pandemic vaccines as a type of seasonal influenza vaccine while others adapted an approval process in place for candidate H5N1 (avian flu) vaccines. The biochemistry of pH1N1 vaccines varied widely, with adjuvanted vaccines (an adjuvant is an inorganic or organic chemical, macromolecule or entire cell of certain killed bacteria which enhance the immune response to an antigen) and vaccines produced using cell-rather than egg-based technology facing more significant regulatory review. In over half of the beneficiary countries, prequalification of a vaccine by WHO was not sufficient to obtain regulatory approval and relatively few countries’ national laws stated that products donated by the United Nations did not require national registration.
Whether GSD or products of GSD can be subject to intellectual property protections is dependent on the laws of the country in which the intellectual property rights are sought and will therefore vary between WHO Member States. The World Intellectual Property Organization has stated that “[n]aturally occurring substances, unaltered or untouched by human technological intervention, are not considered patentable… For a patent to be legitimately granted, there has to be a degree of human intervention leading to an actual invention.”

Obtaining GSD entails additional intellectual steps from simply isolating the virus—e.g., determining the precise order of nucleotides found in a molecule of DNA or RNA. Still, most jurisdictions would deem GSD non-patentable. For example, in Association for Molecular Pathology v Myriad Genetics 569 U.S. 12-398 (2013), the United States Supreme Court held that naturally occurring isolated DNA is not valid patentable subject matter. In an amicus curiae submitted in the same case by the US Department of Justice it was noted that “The chemical structure of native human genes is a product of nature, and it is no less a product of nature when the structure is ‘isolated’ from its natural environment than are cotton fibres that have been separated from the cotton seeds or coal that has been extracted from the earth.” The reasoning in Association for Molecular Pathology v Myriad Genetics 569 U.S. 12-398 (2013) could be extended to viral genetic sequences, including influenza RNA-based viruses, for patents claimed in the United States.

The non-patentability of materials found in nature and, particularly, of DNA can be found in other national laws. For example, Decision 486 of the Andean Community and the Argentine patent law considers non-patentable substances that pre-exist in nature. More specifically, the 1996 Brazilian Industrial Property Code (No. 9.279, 14 May 1996) excludes from patentability living beings or ‘biological materials found in nature’, even if isolated, including the “genome or germplasm” of any living being (article 10.IX). The Biodiversity Law of Costa Rica (1998) establishes the non-patentability of sequences of DNA per se.

In contrast, the European Parliament and Council Directive on the legal protection of biotechnological inventions sought to harmonize the state of the law in the European Union, providing that “biological material which is isolated from its natural environment or produced by means of a technical process” may be patentable, “even if it previously occurred in nature.” This regime expressly includes GSD in its definition of “biological material which is isolated from its natural environment,” providing that GSD may be patentable, “even if it previously occurred in nature.” Like most domestic jurisdictions, European Union Member States typically have numerous additional requirements for a gene sequence to be patentable.

While GSD may not be considered patentable subject matter in most jurisdictions, therapeutic products (or processes) created from biological materials or GSD – such as vaccines – are generally an accepted form of patentable subject matter. The development of an effective therapeutic product may entail innovations that could be protected if the patentability requirements, as applied in the countries where protection is sought, are met. For example, article 27 of the Agreement on Trade-Related Aspects of Intellectual Property Rights requires that a product or process be new, involves an inventive step and have an industrial application to be patentable. But the Agreement does not define what an ‘invention’ is nor how those standards are to be interpreted and applied at the national level.

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42 Ibid.
As such, while patentable subject matter questions may be more settled for products derived from biological materials or GSD, patentability will still be governed by domestic law on a case-by-case basis.

**Patent landscape for vaccines and other products using GSD and synthetic DNA**

It appears likely that the IP environment for vaccines and other products using GSD and synthetic DNA will be complex because other technologies that are, or may be, protected will have to be taken into account in addition to any potential IP related to synthetic DNA and its uses. For instance, for synthetic CVVs for inactivated or live attenuated vaccines, IP covering RG technology will be applicable. Conceivably, patenting of genetic sequences could impede access to and use of genetic sequences in the territories where protection is granted.

**Intellectual Property issues in the PIP Framework**

The PIP Framework does not specifically address issues relating to the management of intellectual property rights. However, section 6.1 of the SMTA 1, which applies to the transfer of PIP biological material within WHO GISRS, provides that: « Neither the provider nor the recipient should seek to obtain any intellectual property rights (IPRs) on the Materials. » Thus, the clear intent of SMTA 1 is to prevent the patenting of PIP biological material within GISRS; the same condition should apply to GSD in cases where protection over such data were available under the applicable law.

In most jurisdictions, influenza GSD would not be considered patentable subject matter. However, innovations from the development of influenza-related products could be protected if the patentability requirements, as applied in the countries where protection is sought, are met. This may lead to a complex IP environment for vaccines and other products using GSD and synthetic DNA.

In accordance with SMTA 1, within GISRS neither the provider nor the recipients of GSD should seek to obtain any intellectual property rights on GSD if protection were available.

### 3. Monitoring, tracing, biosecurity & biosafety implications

#### 3.1. Considering methods to generate, store, retrieve and share GSD, is it possible or feasible to monitor or trace the sharing of GSD? What are the relevant technical, legal or other issues?

Influenza GSD can be shared in the same manner as any other written document, informally or formally, through structured media, such as databases, or through *ad hoc* methods such as email. The author of a sequence may choose to share the sequence information by one or more methods. Under the PIP Framework however, as mentioned, the guiding principles for the terms of reference for GISRS laboratories state that “WHO GISRS laboratories will submit genetic sequences data [of H5N1 or other influenza viruses with human pandemic potential] to GISAID and GenBank or similar databases in a timely manner”. Under the PIP Framework, the core terms of reference for WHO Collaborating Centres for Influenza and for WHO H5 Reference Laboratories require that “WHO GISRS laboratories upload gene sequences of A (H5) and other influenza viruses with pandemic potential to a publicly accessible database in a timely manner”.  

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43 Principle 12 of the PIP Framework generally refers to the global strategy on public health, innovation and intellectual property adopted in resolution WHA61.21.

44 PIP Framework, Annex 4, Principle 9. This principle is directly linked to section 5.2.2 of the Framework where Member States recognized “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”. For further information on public domain databases, see the relevant Glossary entry. Public access is described in the remainder of this section.

45 PIP Framework, Annex 5, (B5)
There are different types of databases that use different methods to permit access to the data that they hold. These can be described as follows:

- **Publicly-accessible unrestricted** databases: These databases allow anybody to submit sequences, download sequences and use sequences for any purpose. Users are not required to register or identify themselves and there are no terms and/or conditions that users must agree to before accessing or using the data. Once downloaded, sequences from such databases may be altered by users, compiled into aggregated sets of sequences and further distributed to third parties freely, without restrictions. Consequently, it would be difficult to monitor downloads from such databases.

- **Publicly-accessible restricted** databases: These databases are accessible to the public, but require users to register and to accept certain terms before they can access and use the database. This may take the form of a ‘user agreement’ that defines conditions for using the GSD. Generally, under such ‘user agreements’, further distribution of GSD is not permitted by that database, unless the prospective recipient is also an authorized user of the database (that is, the prospective recipient has signed the ‘user agreement’). Thus, in most cases, the users of GSD downloaded from publicly-accessible restricted databases cannot further share that data with unidentified, unauthorized third-parties. Because users of publicly-accessible restricted databases must register to gain access to the GSD, this comes close to monitoring the use of GSD as long as users adhere to the ‘user agreement’.

- **Private (or closed) databases**: These databases control access to their data by restricting access to users that have been identified and accepted as users.

Most scientific journals require authors to deposit GSD in a publicly-accessible database before publication of a manuscript.

GSD of PIP biological material can also be generated by non-GISRS laboratories. For example, laboratories receiving PIP biological materials from WHO GISRS, such as virus isolates or extracted RNA, may sequence this material and distribute the sequences to third parties (directly, through publication or by depositing them in databases). In that case, WHO will likely not know of this, and the sharing of such will be more difficult to monitor. Furthermore, with potential future increased use of sequence-based diagnostics, increasing amounts of influenza GSD will be generated with no involvement of the GISRS and may be indistinguishable from GSD generated using PIP biological materials, complicating attempts to determine whether influenza GSD used to produce vaccines has any origin in GISRS activities.

While monitoring and tracing the use of GSD is limited by the medium used to share it, technical mechanisms to trace or monitor downloading of GSD from databases may be implemented. For instance, sharing of GSD could be governed by bilateral material transfer agreements. However, there is a risk that these bilateral agreements would slow down sharing of genetic sequences and the flow of information to WHO, WHO-associated and other laboratories, decision makers and public health professionals; such agreements should therefore be implemented through efficient procedures (such as

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47 Id.
click-wrap agreements) in order to lower that risk. A voluntary system of information regarding use of GSD for commercial purposes could be implemented as well. Any manufacturer, company or organization making use for commercial purposes of GSD arising out of WHO GISRS would have to notify WHO for the purposes of the PIP Framework.

In addition, monitoring could be done through products generated from GSD and for which a patent is applied. Given the difficulty to monitor the use of individual GSD by tracking the access and use of each data source, we could consider the GSD itself to be the unique identifying data. Biological material developed from GSD and analogous to PIP biological material as defined under section 4.1 of the PIP Framework could be considered a PIP biological material and be protectable under the Framework. The use of GSD could be monitored by checking the vaccine genome sequence. It cannot be assumed, however, that patent specifications will necessarily provide the sequence from the vaccine or other products derived therefrom. Verifying that information requires considerable technical expertise and dedication. A mechanism to conduct this task would need to be established for the proposed monitoring to be meaningful. This monitoring could also be done through other mechanisms related to influenza-related products. For instance, the procedure for regulatory approval of such products could be used to monitor and trace the use of GSD, if access to the relevant files were permitted by regulatory authorities.

In regard to secondarily-derived sequences, restrictions could be included in SMTA 2 on sequencing and use of GSD obtained from PIP biological material, but one has to be careful not to impede risk assessment, development of CVVs, research, product development and quality control, for all of which sequencing of the actual material received or amplified in a laboratory may be required.

The objective of benefit-sharing may be met by monitoring use of GSD and/or tracing GSD or by other mechanisms related to influenza-related products.

While monitoring and tracing the use of GSD is limited by the medium used to share it, technical mechanisms to trace or monitor downloading of GSD from databases may be implemented.

GSD of PIP biological material can also be generated by non-GISRS laboratories. In that case, WHO will likely not know of this, and the sharing of such will be more difficult to monitor.

Notwithstanding, there are other potential mechanisms that could be developed to monitor the use of GSD, such as processes related to influenza-related products (e.g. regulatory approval files and patent applications).

3.2. What, in general, are the potential biosecurity issues related to the use of GSD?

Biosecurity

Biosecurity refers to the “institutional and personal security measures designed to prevent the loss, theft, misuse, diversion or intentional release of pathogens and toxins.”\(^{48}\) These measures include measures that deal with access to facilities, storage of materials and data, but also with publication

Biosecurity issues relating to influenza research have been at the forefront of discussions about biosecurity in recent years. More generally with respect to the construction of viruses, the most obvious concerns (in terms both of potential for maliciousness, but also with respect to how discussions about biosecurity play out in public) relate to the resurrection of extinct viruses, the construction of viruses that are typically guarded or viruses for which there is no vaccine or which are drug-resistant.

The construction of influenza viruses, specifically by making copies of known influenza viruses, is relatively easy. Reverse genetics has been used for decades to assemble such viruses in the laboratory. For instance, in 2005 Tumpey et al. adapted the RG system to reconstruct the 1918 influenza virus. Additional improvements to DNA construction technologies will allow ever-easier construction of influenza viruses; one could imagine this being available some day in kit form. In the case of drug-resistant viruses, the ease of construction of influenza viruses (and the ability to introduce mutations into host cell systems) would allow relatively rapid testing of undirected mutations.

In the context of synthetic biology technologies, the most obvious threat is the use of GSD to recreate a biologically viable virus to initiate new infections. Regardless of whether a virus sample or GSD is the originating source in the development of a bioweapon, however, successful use is contingent on technological ability. Technical capacities would require the ability to convert sequencing data to biological materials. In addition, once badly intentioned actors gained access to hazardous biological materials, they would need the capacity to “weaponize” those materials, for example, by rendering them more rapidly and efficiently dispersible.

The first step for carrying out the construction of synthetic viruses (any virus, for any purpose) would be to make or order stretches of DNA (to be combined to create a complete influenza genome). In general, at the moment, it is extremely difficult to make long stretches of DNA in a standard laboratory; this would therefore require ordering these pieces from a company specialized in the production of synthetic DNA. For the most part, these companies state that they screen the sequence of the orders coming in to ensure that they are not filling orders for pathogens, and that they adhere to all domestic and international rules for export. Whether the intent of users is malicious is a different question and requires more effort from the companies (e.g., assuring that the order comes from a legitimate customer who has appropriate permissions to obtain such sequences).

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50 For instance: studies about pandemic flu virus extracted from the body of persons dead from the 1918 pandemic flu; publications of papers on the genetic engineering of H5N1 avian influenza virus for purpose of analyzing the genetic determinants of virus transmissibility; the perspective of similar studies being done with the recently detected H7N9 influenza virus.
55 The emergence of drug resistant microbes happens with some regularity during epidemics, by the misuse of antimicrobials, and in general in nature. We do not, however, fully understand the mechanisms of microbe resistance to antimicrobials so it would at this time be difficult to design directly a drug-resistant virus.
Influenza genes, however, are relatively small; although a considerable level of skill is required, it is quite possible that researchers are currently generating synthetic viruses without going through these synthesis companies, either by ordering instead oligonucleotides (which are extremely difficult or impossible to screen), or by synthesizing the oligonucleotides themselves on machines located in their laboratories or departments. There is ongoing concern that individuals with malicious intent might use desktop oligonucleotide synthesizers to construct pathogens; therefore monitoring by the companies making very long genomic DNA may only offer a temporary solution.

From a biosecurity perspective, it may be easier to control the custody of a physical object, such as a virus sample, than the custody of data. Large magnitudes of data can be readily disseminated in electronic form, such as through the Internet. However, it is more difficult to convert complex data sequences to malicious use than to use biological materials maliciously. Nonetheless, these issues already exist for all-publicly available GSD and are already under considerable scrutiny within the context of dual-use research of concern. It is hard to see how any PIP GSD would provide an increased risk over what is currently possible.

**Biosafety**

Biosafety refers to “the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release.”\(^57\) In the context of influenza research and, the development and production of influenza product, there are concerns about accidents that could endanger laboratory workers or people in wider communities around laboratories. As well, a “do-it-yourself” community is emerging in life sciences (e.g., individuals or groups setting up laboratories in their garages, or in shared spaces\(^58\)). The concerns within and about both of these groups is a lack of training or awareness of how to conduct research safely.\(^59\)

From a biosafety standpoint, GSD has potential advantages over the sharing of virus samples, as it mitigates the risk of the inadvertent release of the infectious agent by limiting access to the original biological agent; and by restricting access of dangerous influenza samples to authorized laboratories involved in vaccine development that have adequate high-level security. Furthermore, by reducing the need to transport influenza virus with pandemic potential, the use of GSD could be seen as a way to improve the safety of the production of influenza vaccines, antivirals and diagnostics.

The biosafety benefits of GSD over biological samples may be counteracted, however, if it results in broader access to sequencing and other information about the virus by laboratories with inadequate containment or other biosafety precautions – that otherwise would not have had access to virus samples – potentially creating, or otherwise obtaining, biological materials derived from the sequencing data.

**Biosecurity/biosafety and databases**

Biosafety/biosecurity concerns related to the use of GSD are directly linked to ease of access to the sequences. To properly assess biosecurity/biosafety risks, the various aspects related to the free and easy circulation of GSD must be taken into account. As the PIP Framework requires that WHO


\(^{58}\) See for example, DIY bio (at diybio.org) and Genspace (at genspace.org).

GISRS laboratories post GSD in public-domain and publicly-accessible database, the collection, storage, consultation and extraction of GSD will depend on the terms of use of those databases. Therefore, when assessing the terms of use of those databases from a biosecurity perspective, consideration should be given as to whether they restrict or place any conditions on the use and distribution of GSD.

However, assessing those databases will require careful evaluation and balancing two important values that are sometimes in tension: (1) equity that is advanced by greater sharing of biological materials, sequencing data, and the benefits of vaccine research and development; (2) and security which is advanced by limiting access to biological materials and sequencing data. As the dissemination of electronic data is inherently more difficult to control than biological materials, any possible restrictions on accessing information may not be effective in keeping GSD within vaccine or treatment focused research laboratories.

Biosafety/biosecurity concerns related to the use of GSD are directly linked to ease of access to the sequences and are contingent on technological ability.

3.3. What are the prospects for influenza GSD to be used to develop non-influenza related products?

Influenza GSD may be used to develop non-influenza related products, e.g. viral vectors. For many of these applications, the use of GSD from influenza viruses with pandemic potential will not be required and other, more easily accessible viruses (such as seasonal influenza viruses or laboratory-adapted strains) that are not covered by the PIP Framework may be used instead. Therefore, GSD as covered by the PIP Framework are likely to be of minor importance in this area.

There is some potential that the use of large scale influenza GSD will provide the data backdrop for novel computational methods of predicting, monitoring and providing models for control measure assessment and that such computational tools and systems could be commercialized and used for other infectious diseases.
ANNEX 1

LIST OF ABBREVIATIONS AND ACRONYMS

CC or WHO CC: World Health Organization Collaborating Centre

cDNA: complementary DNA

CVV: Candidate Vaccine Virus

DDBJ: DNA DataBank of Japan

DNA: deoxyribonucleic acid

EMA: European Medicines Agency

ENA: European Nucleotide Archive

FDA: United States Food and Drug Administration

GISAID: Global Initiative on Sharing All Influenza Data

GISRS or WHO GISRS: Global Influenza Surveillance and Response System

GSD: genetic sequence data

IVPP: Influenza viruses with pandemic potential

IP: Intellectual Property

IPR: Intellectual Property Rights

MDCK: Madin-Darby Canine Kidney cell

mRNA: messenger RNA

PIP AG: PIP Framework Advisory Group

PIP BM: Pandemic Influenza Preparedness Biological Material

PIP Framework: Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits

PIP GSD: Genetic sequence data generated from PIP BM

RG: Reverse genetics

RNA: Ribonucleic acid

SMTA 1: Standard Material Transfer Agreement 1

SMTA 2: Standard Material Transfer Agreement 2

VLP: Virus-like particle

WHA: World Health Assembly

WHO: World Health Organization
Glossary of terms

**Adjuvant/adjuvanted vaccine:** A substance (e.g. aluminum salt) that is added during vaccine production or mixed with the vaccine antigen after production to increase the body's immune response.\(^{60}\)

**Antigen:** Any substance capable of eliciting an adaptive immune response, including the production of antibodies.

**Antigenically similar/appropriate:** A CVV that stimulates, *in vitro*, a human immune response measurably similar to currently circulating influenza viruses. In the context of vaccine production, testing for antigenic appropriateness ensures that the CVV will stimulate an immune response in vaccinated individuals that will protect them against the circulating influenza virus.

**Backbone:** Of the 8 influenza gene segments, the backbone consists of the 6 segments that are not the hemagglutinin (HA) and neuraminidase (NA) gene segments. These backbone gene segments originate from influenza viruses that have been adapted to grow efficiently into chicken eggs or mammalian cells.

**Candidate vaccine virus (CVV):** Influenza virus that has been developed or adapted to use for the production of a seasonal or pandemic influenza vaccine. Most CVVs currently used for vaccine production have been produced by GISRS.

**cDNA (complementary DNA):** Complementary DNA molecule generated by reverse transcription of viral RNA. cDNA will contain the same genetic information as the viral RNA it is made from.

**Cell-based vaccine:** Vaccines grown in cultured cells of mammalian origin (such as MDCK cells) instead of in chicken eggs.\(^{61}\)

**Classical reassortment:** A method to generate candidate vaccine viruses for influenza vaccine production that relies on gene reassortment. Gene reassortment involves the inoculation of chicken eggs or cultured cells with two or more influenza viruses: for instance, the circulating wild-type influenza virus and an attenuated human virus that has been selected for its capacity to grow efficiently in eggs. The resulting candidate vaccine virus will allow the manufacturer to produce vaccines against the circulating wild-type virus.

**Conserved regions/epitopes:** Regions of, for example, a gene sequence or protein sequence which are identical or similar and undergo limited genetic variation over time. Due to these characteristics, conserved regions are currently used in efforts to develop universal vaccines.

**Desktop oligonucleotide synthesizers:** An oligonucleotide synthesizer is a device that is used to generate short sequences of DNA or RNA. A desktop synthesizer can be the size of an inkjet printer (or smaller) and can be used by individuals to synthesize influenza gene sequences.

**Dual-use research of concern:** “Research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, […]”.\(^{62}\)

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\(^{60}\) Center for disease control and prevention (CDC), *Vaccines and Immunization, Glossary*, available at http://www.cdc.gov/vaccines/about/ terms/glossary.htm#c


\(^{62}\) National Science Advisory Board for Biosecurity, *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the*
**Egg-based vaccine:** Vaccine grown in embryonated chicken eggs.

**Fusion proteins:** See Recombinant proteins.

**GenBank:** Genetic sequence database hosted by the US National Center for Biotechnology Information and the US National Institute of Health. It is a collection of publicly available DNA sequences. GenBank is part of the International Nucleotide Sequence Database Collaboration, which comprises the DNA DataBank of Japan (DDBJ), the European Molecular Biology Laboratory (EMBL), and GenBank at NCBI. These three organizations exchange data on a daily basis.63

**Genes:** The basic physical and functional unit of heredity. Genes contain the information that determines the biological characteristics of an organism.64 The influenza genome contains 11 genes encoded in 8 RNA segments, which contain around 14,000 nucleotides.

**Genetic sequence data (GSD):** 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 (from section 4.2 of the PIP Framework).

**GISAID (Global Initiative on Sharing All Influenza Data):**
The GISAID Initiative provides access to the EpiFlu™ Database, which was developed by the Max-Plank-Institut für Informatik and is hosted by the German Federal Ministry of Food and Agriculture. The EpiFlu™ Database is a publicly-accessible collection of influenza sequences containing associated metadata, both clinical & epidemiological.65

**GISRS (Global Influenza Surveillance and Response System):** Global network of laboratories coordinated by WHO that monitors the emergence and evolution of influenza viruses and provides recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment.66

**Hemagglutinin (HA):** A protein on the surface of the influenza virus that allows the virus to attach itself to a cell in the upper and lower respiratory tracts and penetrate it. Referred to as the ‘H’ in the nomenclature of influenza viruses.

**High-yield influenza reassortant/high-growth reassortant:** Influenza virus produced through gene reassortment (see definition of classical reassortant) by assembling HA and NA gene segments from a wild-type virus with a backbone which has been selected for its capacity to grow efficiently in eggs.

**Inactivated vaccine:** A vaccine that contains killed virus components, which cannot cause disease.

**Influenza virus with pandemic potential:** As defined under section 4.2 of the PIP Framework, it refers to any wild-type virus that has been found to infect humans and that has a hemagglutinin antigen that is distinct from those of seasonal influenza viruses so as to indicate that the virus has the potential to be associated with pandemic spread within human populations with reference to the International Health Regulations (2005) for defining characteristics.

**Live attenuated vaccine:** A vaccine in which a live influenza virus is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of a disease.67

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65 Global Initiative on Sharing all Influenza Data (GISAID), available at http://www.gisaid.org/
67 Center for disease control and prevention (CDC), Vaccines and Immunization, Glossary, available at http://www.cdc.gov/vaccines/about/terms/glossary.htm#c
Madin-Darby Canine Kidney (MDCK) cells: A type of cell line used, *inter alia*, to produce cell-based vaccine. They allow growing candidate vaccine viruses for use in cell-based vaccine production.

Material transfer agreement: A legally-binding contract that governs the transfer of biological material or data between two or more parties.\(^6^8\)

mRNA (messenger RNA): RNA molecule that carries the genetic information necessary to make a protein.

Mutation: A change in the gene sequence.

Neuraminidase (NA): An important surface structure protein of an influenza virus particle. The NA enables the release of the virus from the host cell to infect new cells within the respiratory tract. Referred to as the “N” in the nomenclature of influenza viruses.

Nucleic acid: A type of molecule (DNA or RNA) found in cells and viruses responsible for the storage and expression of genetic information. Influenza viruses contain RNA molecules.

Oncolytic virus: A virus that infects and kills cancer cells.

Plasmid: A small piece of circular DNA that can be used to insert/transfect influenza viral cDNA into cell lines in order to express viral proteins.

**PIP Biological Material (Pandemic Influenza Preparedness biological material):** Defined under section 4.1 of the PIP Framework for the purpose of the application of the Framework and its annexes. It includes human clinical specimens; virus isolates of wild type human H5N1 and other influenza viruses with 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 reassortment; 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.

Primer: A short DNA sequence that serves as a starting point for DNA synthesis. Primers are used in many laboratory techniques, such as the polymerase chain reaction (PCR) technique and DNA sequencing.\(^6^9\)

Probe: A single-stranded sequence of DNA or RNA that is radioactively or chemically-labelled and is used to search for its complementary sequence in a sample genome.

Public domain database: Public domain databases, such as GenBank, were created to allow free and unrestricted access to published genetic sequence data. Sequences gathered in such databases were free of proprietary rights and thus in the public domain. Nowadays however, GenBank also hosts unpublished data and sequence data from patents issued by the United States Office of Patents and Trademarks.\(^7^1\) (which may be claimed in patents and thus subject to proprietary rights).\(^7^2\)

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**Recombinant protein:** Proteins expressed from recombinant DNA, such as those engineered by fusing several genes together. These recombinant proteins retain some of the structural characteristics of the original proteins encoded by the fused genes.

**Market authorisation:** Process by which a pharmaceutical product (e.g. vaccine or antivirals) is evaluated in order to determine whether it fulfils the necessary requirements (usually based on quality, safety and efficacy) to be sold in a particular regional or national market.

**Regulatory Approval:** See Market authorisation.

**Reverse genetics technology:** Method for generating, for example, candidate vaccine viruses that involves the insertion of viral nucleic acid (usually through the use of a vector) in vaccine-approved cells (see definition below). Replication of the virus then takes place inside the cells, allowing production of candidate vaccine viruses or viral proteins.

**RNA-based virus:** Virus whose genome is made of RNA, instead of DNA. Influenza viruses are RNA-based viruses.

**Standard Material Transfer Agreement 1 (SMTA 1):** Found under annex 1 of the PIP Framework, SMTA 1 is a legally-binding contract that governs the transfer of PIP biological material between WHO GISRS laboratories.

**Standard Material Transfer Agreement 2 (SMTA 2):** Found under annex 2 of the PIP Framework, SMTA 2 is a legally-binding contract that governs the transfer of PIP biological material from WHO GISRS to outside entities, such as influenza vaccine, diagnostic and pharmaceutical manufacturers, as well as biotechnology firms, research institutions and academic institutions.

**Seed material:** see Candidate vaccine viruses. Viruses used to produce a vaccine.

**Site-directed mutagenesis:** Laboratory method that is used to deliberately induce a mutation at a specific location of a gene sequence.

**Synthetic DNA (protein, CVV or vaccine):** DNA molecule created through chemical synthesis using genetic sequence data. Generation of synthetic DNA does not require physical material. Can also refer to semi-synthetic proteins.

**Transfect:** Process by which viral cDNA is inserted into a cell.

**Universal influenza vaccine:** A vaccine developed to protect against all sub-types of influenza A viruses.

**Vaccine efficacy:** A measure used to define the reduction in the incidence of disease after vaccination.

**Vector:** Vehicle for delivering foreign genetic material such as DNA into a cell, where it will be replicated and/or expressed. Examples of vectors include plasmids and modified viruses.

**Virulence:** The ability of the virus to cause disease. The level of virulence may vary from one influenza virus to the other.

**Virus-like particle:** Structure composed of viral proteins that mimics the structure of a complete virus but lacks the viral genome. 73

**WHO Prequalification:** WHO prequalification of medicines is a service provided by WHO to assess the quality, safety and efficacy of medicinal products, including vaccines or antiviral medicines, for purchase by UN agencies. 74


ANNEX 3

METHODOLOGY FOR THE DEVELOPMENT OF THE REPORT

- TEWG experts selected one or more of the technical questions framing the Discussion and provided written contributions to the Secretariat. In some instances, experts worked together in small groups.
- The experts met for the first time, via teleconference, on 5 December 2013 to discuss the TEWG’s method of work.
- On 22 January 2014, an invitation to provide input on the issues related to the handling of genetic sequence data under the PIP Framework was sent to the following industry associations, civil society and other organizations: AdvaMedDX, Berne Declaration, Biotechnology Industry Organization (BIO), Developing Countries Vaccine Manufacturers Network (DCVMN), GenBank, GISAID, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), International Pharmaceutical Students' Federation (IPSF), Knowledge Ecology International, and Third World Network (TWN). The deadline for receipt of contributions was set for 15 March 2014.
- On 25 February 2014, a preliminary draft of this Report was sent to TEWG experts for discussion during a teleconference meeting that was held on 3 March 2014. Experts were requested to submit revisions no later than 13 March 2014.
- In addition, to clarify some of the more technical terms in the preliminary draft Report, the Secretariat developed a ‘List of abbreviations and acronyms’ and a ‘Glossary of terms’, which are found at Annex 1 and 2 respectively.
- Contributions were received from NCBI/GenBank, IFPMA and BIO, and TWN (on 15 March 2014), from Novartis Vaccines (on 24 March 2014) and from GISAID (on 4 April 2014).
- The TEWG met in Geneva on 8 April 2014 to discuss the preliminary draft Report.
- The TEWG met with the PIP Advisory Group on 9 April to present the main findings from the preliminary Report.
- Following these 2 meetings, further comments and revisions provided by the experts were integrated to finalize this Report.
### 1) List of TEWG Experts

<table>
<thead>
<tr>
<th>Advisory Group members</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Pr Didier Houssin, TEWG Chair</td>
<td>President, French Evaluation Agency for Research and Higher Education (AERES), France</td>
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<td>Dr William Ampofo, AG Chair</td>
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<td>Former Director, International Operations, Medicines for Malaria Venture, Public Health Specialist, India</td>
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<tr>
<td>Dr Pathom Sawanpanyalert</td>
<td>Deputy Secretary General, Food and Drug Administration, Thailand Ministry of Public Health, Thailand</td>
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2) **Expert Selection process**

- The PIP Advisory Group specified that experts should be selected based on their expertise in law, science, public health and/or biosecurity.
- TEWG experts were therefore selected for their expertise in the following fields: influenza research, vaccine design and/or new technologies for biological synthesis; intellectual property law and innovations; public health policy, ethics and/or biosecurity.
- Because some of these fields are relatively new, the number of available experts was limited.
- Experts from the private sector, academia and/or civil society were sought in order to ensure that the TEWG could develop a solid understanding of possible GSD implications for the vaccine and diagnostic industry in general, and product developments in particular.
- Five members of the Advisory Group also participated, on a voluntary basis, to provide the PIP Framework perspective.
- Due to the complexity of the issues to be discussed, fluency in English was considered a basic requirement for experts.

3) **Declarations of Interests by TEWG experts**

- The TEWG did not provide any recommendations to the PIP AG, WHO, Member States or other stakeholders. Likewise, the TEWG did not provide normative assessment or policy advice. Its sole responsibility was to provide information on the “scientific, technical, operational and intellectual property implications of using influenza virus GSD rather than influenza viruses”. It was determined that experts with the broadest perspective possible on these issues were necessary to allow a broad fact-finding.
- Notwithstanding the limited mandate of the TEWG, all TEWG participants were asked to complete a Declaration of Interests to assess real, potential or actual conflicts of interests in relation to the work of the TEWG.
- The following interests and/or affiliations were disclosed:

<table>
<thead>
<tr>
<th>Name</th>
<th>Interest declared</th>
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<tbody>
<tr>
<td>Dr William Ampofo</td>
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<td>Dr Othmar Engelhardt</td>
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<td>Dr Rainer Engelhardt</td>
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<tr>
<td>Dr Michele Garfinkel</td>
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<tr>
<td></td>
<td>Grant from the US Department of Energy to study US regulatory issues for synthetic biology</td>
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<td>Pr Didier Houssin</td>
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<td>Pr Paul Kellam</td>
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<td></td>
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</tbody>
</table>
| Dr Gary Nabel | • Full-time employee of Sanofi  
|              | • Has Sanofi stock over USD 10k  
|              | • Listed as an inventor on IP held by NIH |
| Dr Rino Rappuoli | • Full-time employee of Novartis |
| Dr Pathom Sawanpanyalert | • Member of the GISAID Scientific Advisory Council |

- The foregoing interests declared by TEWG participants were reviewed by WHO and determined not to present a conflict of interest with the mandate of the TEWG. However, as they were deemed relevant to the work of the TEWG, they were disclosed to the participants.
- No other interests declared by TEWG experts were deemed relevant to the work of the group.